

EXCITON COUPLED CIRCULAR DICHROISM: APPLICATIONS FOR THE DETERMINATION OF
ABSOLUTE STEREOCHEMISTRY OF ORGANIC MOLECULES AND STERIC AND ELECTRONIC
MODULATIONS OF PORPHYRIN TWEEZER SYSTEMS

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ABSTRACT

EXCITON COUPLED CIRCULAR DICHROISM: APPLICATIONS FOR THE DETERMINATION OF ABSOLUTE STEREOCHEMISTRY OF ORGANIC MOLECULES AND STERIC AND ELECTRONIC MODULATIONS OF PORPHYRIN TWEEZER SYSTEMS

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Exciton coupled circular dichroism (ECCD), a sub-discipline of electronic circular dichroism, is a non-empirical, chiroptical method by which the absolute stereochemistry of chromophoric, chiral molecules can be determined. The sign of the ECCD signal can be directly correlated to the helical arrangement of the chromophores of the molecule thereby allowing for the assignment of configuration of the molecule. The end goal of our research is to develop ECCD host systems capable of accepting a wide range of chiral guest molecules and provide consistent and reliable ECCD results. The research disclosed, being multifaceted, explored several aspects of determination of absolute chemistry using porphyrin tweezer host systems as reporters of chirality. Specifically, the mechanism for chirality transfer from the chiral guest molecule to the porphyrin tweezer host molecule, development of ECCD protocols for different classes of guest molecules and evolution of new guest molecules were explored.

The mechanism of chirality transfer was interrogated using a highly fluorinated alkyl substituted porphyrin tweezer. Results of the study indicate that alkyl substituents reduce interaction between the host and guest which in turn, reduce the efficiency of the transfer of chirality from the guest to the porphyrin tweezer. To determine if the methylene linker between the porphyrins of the tweezer played a role in the transfer of chirality from guest to host, a series of porphyrin tweezers with varied linker lengths were synthesized. The results of

this study showed that the length of the linker could promote or inhibit formation of the host-guest complex.

Using the porphyrin tweezer host systems, ECCD protocols for determination of absolute stereochemistry of chiral pyridyl alcohols, epoxy amides and aziridine amides were developed. These methodologies are capable of reliably reporting the stereochemistry of the guest molecule at micromolar concentrations. Finally, a benzoxazole tripodal system was synthesized as a host molecule for chiral ammonium salts. NMR analysis indicated that the host-guest complex did form although an ECCD signal was not observed. These encouraging results create a platform for future work into tripodal based host systems for ECCD.

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For my family

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This dissertation summarizes the work that I conducted in the laboratory over the past six years but gives no indication of the support network of family, friends, mentors and coworkers that made this work possible.

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KEY TO ABBREVIATIONS AND SYMBOLS

α	Angle of rotation
$[\alpha]$	Specific rotation
$[\alpha]_D$	Specific rotation at 589 nm
Å	Angstrom
AcCl	Acetylchloride
AcOH	Acetic acid
$[(\text{allyl})\text{PdCl}]_2$	Allylpalladium (II) chloride dimer
9-AMA	9-anthrylmethoxyacetic acid
aq	Aqueous
Ar	Aryl, Argon
B	Magnetic field
$\text{BH}_3 \cdot \text{SMe}_2$	Borane dimethylsulfide
$\text{BF}_3 \cdot \text{OEt}_2$	Boron trifluoride diethyl etherate
bpy	Bispyridine
Bn	Benzyl
Boc	<i>tert</i> -butyloxycarbonyl
$(\text{Boc})_2\text{O}$	<i>tert</i> -butyloxycarbonyl anhydride
BOP	Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexa-fluorophosphate
brsm	Based on recovered starting material
<i>t</i> Bu	<i>tert</i> -butyl

BUDAM	tetra- <i>tert</i> -butyldianisylmethyl
<i>n</i> BuLi	<i>n</i> -butyllithium
<i>t</i> BuOH	<i>tert</i> -butanol
<i>t</i> BuOOH	<i>tert</i> -butylhydroperoxide
<i>t</i> BuNH ₃ I	tert-butylammonium iodide
Bz	Benzoyl
<i>c</i>	Speed of light
C	Celcius
C ₃ F ₇	10,15,20-tris(2,2,3,3,4,4,4-heptafluoropropyl)-5-(4-benzoate)porphyrin
C ₅ H ₁₁ MgBr	Pentylmagnesium bromide
CaH ₂	Calcium hydride
CBS	Corey-Bakshi-Shibata
CD	Circular dichroism
CDM	Piezoelastic modulator
<i>p</i> -Chloranil	tetrachloro-1,4-benzoquinone
C-H	Carbon-Hydrogen bond
CH ₂ Cl ₂	Dichloromethane
cm	Centimeter
Cu(ClO ₄) ₂	Copper (II) perchlorate
CuI	Copper Iodide
Cu(OAc) ₂ •H ₂ O	Copper (II) acetate dihydrate
Δ	Change
d	Doublet

dd	Doublet of doublets
ddd	Doublet of doublet of doublets
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	<i>N,N</i> -4-(dimethylamino)pyridine
DMA	<i>N,N</i> -dimethylacetamide
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	Dimethylsulfoxide
DPM	Dipyrromethane
dt	Doublet of triplets
ϵ	Extinction Coefficient
E	Energy
ECCD	Exciton Coupled Circular Dichroism
ECD	Electronic Circular Dichroism
EDC	<i>N,N'</i> -diethylcarbodiimide
edtm	Electric transition dipole moment
ee	Enantiomeric excess
e.g.	exempli gratia
EI	Electron impact
equiv	Equivalents
etc	Et cetera

Et ₄ NI	Tetraethylammonium iodide
Et ₂ O	diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
Et ₂ Zn	Diethylzinc
eV	Electron volts
g	Gram
h	Hour
H	proton
H ₂	Hydrogen
HCO ₂ H	Formic acid
H ₂ O	Water
H ₂ O ₂	Hydrogen peroxide
HCl	Hydrochloric acid
H ₂ SO ₄	Sulfuric acid
Hz	Hertz
HMPA	Hexamethylphosphoramide
HRMS	High-resolution mass spectrometry
I	Intensity of light
I ₂	Iodine
i.e	id est
InCl ₃	Indium (III) chloride
IR	Infrared spectroscopy

Ir	Iridium
[Ir(cod)Cl] ₂	Cyclooctadienyliridium (II) chloride dimer
<i>J</i>	Coupling constant
K _a	Constant of association, binding affinity, binding constant
K ₂ CO ₃	Potassium carbonate
KHMDS	Potassium hexamethyldisilazide
KOAc	Potassium acetate
λ	Wavelength
λ _{max}	Absorption maximum
L	Liter
LAH	Lithium aluminum hydride
LCPL	Left-circularly polarized light
LiBr	Lithium bromide
LPL	Linearly polarized light
LUMO	Lowest Unoccupied Molecular Orbital
<i>m</i>	Net magnetic transition dipole moment
m	Multiplet
M	Molar
M ⁺	Mass with positive charge
[M+H] ⁺	Mass + hydrogen with a positive charge
m/z	Mass per charge
MCH	Methylcyclohexane
Me	Methyl

MEDAM	tetra-methyldianisylmethyl
MeMgBr	Methylmagnesium bromide
(MeOCO) ₂ CH ₂	Dimethylmalonate
MeOH	Methanol
MeNO ₂	Nitromethane
mg	Milligram
MgBr ₂	Magnesium bromide
MHz	Megahertz
min	Minute
mL	Milliliter
mmol	Millimole
MnO ₂	Magnesium dioxide
mol	Mole
MPA	α-methoxy-phenylacetic acid
mtdm	Magnetic transition dipole moment
N ₂	Nitrogen
NaBAr _F	Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
NaCN	Sodium cyanide
NaH	Sodium hydride
NaHCO ₃	Sodium bicarbonate
NaOH	Sodium Hydroxide
Na ₂ SO ₄	Sodium sulfate
nd	not determined

NH ₄ Cl	Ammonium chloride
NH ₄ OAc	Ammonium acetate
NH ₄ SCN	Ammonium thiocyanate
NiCRAL	Liganded nickel containing Complex Reducing Agents
Ni(OAc) ₂	Nickel (II) acetate
Ni(PPh ₃) ₂ Cl ₂	bis-tetraphenylphosphine nickel (II) chloride
nm	nanometer
NMR	Nuclear magnetic resonance
O ₂	Oxygen
OR	Optical Rotation
ORD	Optical Rotatory Dispersion
P1	Porphyrin 1
P2	Porphyrin 2
PCC	Pyridinium chlorochromate
Pd	Palladium
Pd/C	Palladium on Charcoal
Pd(OH) ₂ /C	Palladium hydroxide on Charcoal
Pd(PPh ₃) ₄	Palladium (0) tetrakis(triphenylphosphine)
PG	Protecting group
Ph	Phenyl
PhCl	Chlorobenzene
PhMgBr	Phenylmagnesium bromide
Ph ₂ PNEt ₂	<i>N,N</i> -diethylaminodiphenylphosphine

Ph ₃ COOH	Trityl hydroperoxide
PMT	Photomultiplier tube
PPh ₃	Triphenylphosphine
POCl ₃	Phosphorous oxychloride
ppm	Parts per million
<i>n</i> PrNH ₂	<i>n</i> -Propylamine
py	Pyridine
PyBOX	2,6-Bis[(4 <i>R</i>)-(+) -isopropyl-2-oxazolin-2-yl]pyridine
qt	quartet of triplets
<i>R</i>	Rotational strength
RCPL	Right-circularly polarized light
Rh ₂ (OAc) ₄	Rhodium(II) acetate dimer
[Rh ₂ (O ₂ CCF ₃) ₄]	Rhodium(II)trifluoromethylacetate dimer
rt	Room temperature
s	Singlet
sat	Saturated
SES	Trimethylsilylethanesulfonyl
t	Triplet
TBP	10,15,20-tris(3,5-ditert-butylphenyl)-5-(4-benzoate)porphyrin
TBS	<i>tert</i> -butyldimethylsilyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

THP	Tetrahydropyran
Ti(OiPr) ₄	Titanium tetraisopropoxide
TLC	Thin-layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TMsP	10,15,20-tris(2,4,6-trimethylphenyl)-5-(4-benzoate)porphyrin
TPFP	10,15,20-tris(pentafluorophenyl)-5-(4-benzoate)porphyrin
TPP	10,15,20-trisphenyl-5-benzoate porphyrin
Trityl	Triphenylmethyl
Ts	Tosyl, toluenesulfonyl
TsCl	Tosylchloride
TsDPEN	<i>N-p</i> -Tosyl-1,2-diphenylethylenediamine
Tz	Tweezer
μ	Net electric transition dipole moment
μL	Microliter
Unsub	Unsubstituted porphyrin: 5-(4-benzoate)porphyrin
UV-Vis	Ultraviolet-Visible Spectroscopy
VCD	Vibronic Circular Dichroism
XRD	X-Ray Dispersion
xs	Times
Zn	Zinc
Zn(OAc) ₂	Zinc (II) acetate
Zn(OTf) ₂	Zinc (II) triflate

Chapter I

Chirality and Methods of Determining Absolute

Stereochemistry

I.1: Introduction of Chirality

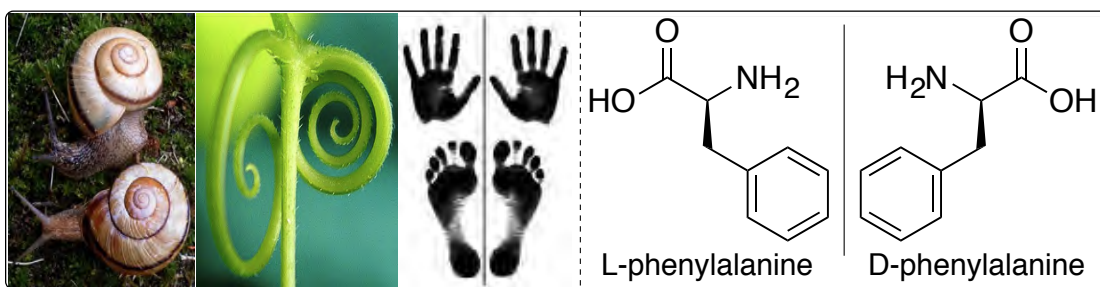


Figure I.1: Examples of chiral entities ranging from the macroscale (hands and feet) to the microscale (chiral amino acids).¹⁻³ For interpretation of the references to color in this and all other figures, the reader is referred to the electronic version of this dissertation.

Chirality is defined as any entity lacking an element of symmetry or having a non-superimposable mirror image. These include familiar objects such as our hands and feet¹ and the chiral amino acids necessary for life. Other, perhaps less often thought of objects would include the spiral inscribed in snail shells² or the curl of grape vines³ (Figure I.1). The concept of chirality in organic molecules dates back to the 1800s. In 1811, French physicist François Arago observed the rotation of plane polarized light through quartz crystals, a phenomenon now known as optical rotation.⁴ In 1815, Jean-Baptiste Biot reported optical rotation in liquid and gaseous chiral media. In 1849, Louis Pasteur studied the both the crystalline and solution

forms of ($\pm$)-tartaric acid. When crystallized, Pasteur found two distinct crystal types. After a careful and tedious manual separation of the crystals, a solution of each was made and observation of the optical rotations of the two solutions showed signals with equal intensity but opposite sign. He correctly attributed the difference in the crystal structures and optical rotation of ($\pm$)-tartaric acid to different arrangements of groups in space. He called this handedness or dissymmetry. Due to his discovery, Pasteur is accredited with the discovery of molecular chirality.^{4,5} Then in 1874, van't Hoff and Le Bel hypothesized that optical rotation resulted from the three dimensional arrangement of substituents about a tetrahedral carbon. However, it was not until 1894, in a lecture by Lord Kelvin that the terms “chiral” and “chirality” were used to describe such molecules.⁵

The most familiar type of chirality in organic molecules, point chirality, occurs when a tetrahedral atom, typically carbon, has four different substituents (α -methylbenzylamine, Figure I.2 A). Although carbon is the most common center of point chirality, other atoms such as the sulfur of a sulfoxide or a nitrogen with restricted inversion can also serve as centers of point chirality. The three dimensional arrangement of the substituents about the chiral center can then be described as *R* or *S* configuration using the priority rules set by Cahn, Prelog and Ingold.⁶

Substituted allenes (2,3-pentadiene, Figure I.2 B) and biphenyls (6,6'-dinitrobiphenyl-2,2'-dicarboxylic acid, Figure I.2 C) are classical examples of axial chirality in organic chemistry. These molecules contain an axis of chirality as opposed to a stereogenic center as with point chirality. Assignment of configuration for these molecules considers each carbon separately. The substituents of each carbon are assigned priority based on the Cahn-

Ingold-Prelog, *R* or *S* configuration is assigned based on arrangement of the high priority groups relative to one another. A special type of axial chirality, helical chirality, occurs with molecules that form a screw shape or a helix (hexahelicene, Figure I.2 D). These molecules are assigned *P* or *M* helicity if molecule resides as a right-handed or left-handed helix, respectively.⁷

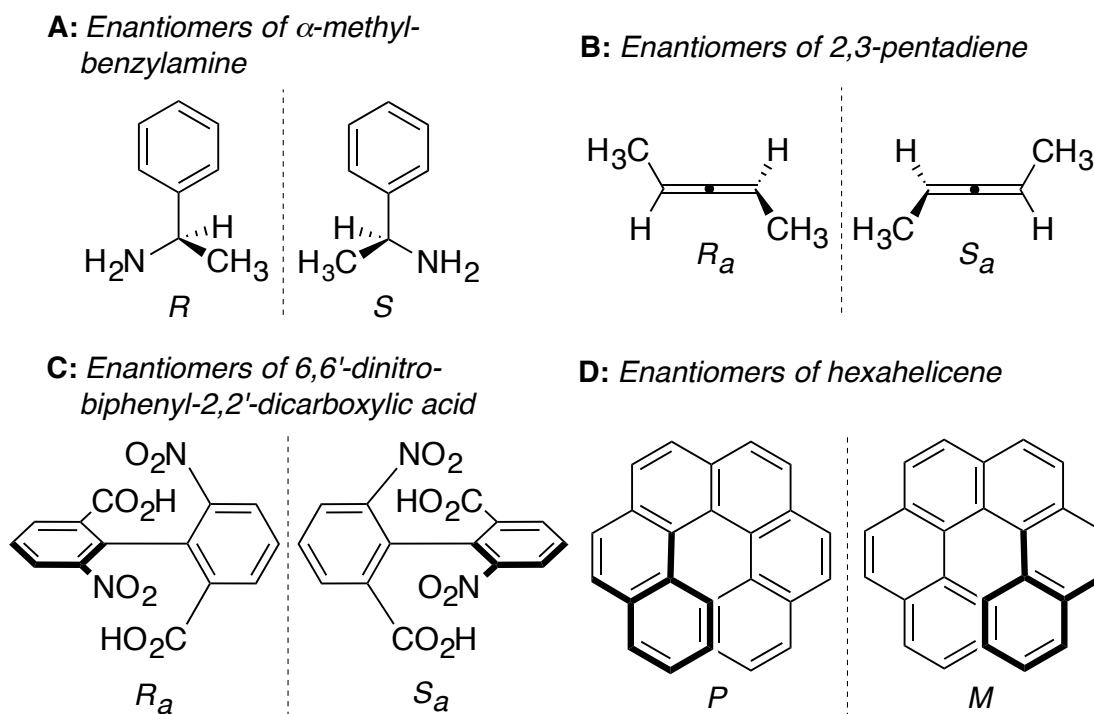


Figure I.2: The figures above represent the four major types of chirality. **A:** A tetrahedral carbon with four different substituents is an example of point chirality. The configuration of the carbon is indicated with the Cahn-Prelog-Ingold designation of *R* or *S*.⁶ **B-D:** These represent three different types of axial chirality. For **B** and **C** the Cahn-Prelog-Ingold designation of *R_a* or *S_a* describe the arrangement of the molecules with the subscript *a* indicating axial chirality. **D** is an example of helical chirality. The assignment of *P* and *M* indicate a right-handed or left-handed helix, respectively.⁷

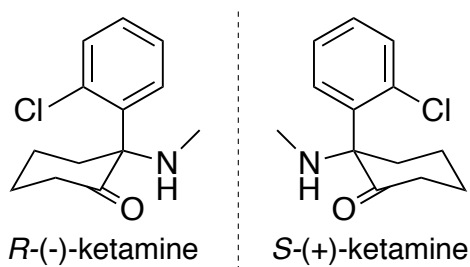


Figure I.3: The two enantiomers of the drug ketamine known to have distinctly different effects on the human body.⁸

The importance of determining absolute configuration has gained significance particularly with the growth of the pharmaceutical industry. A 2002 report indicated that 56% of drugs sold were chiral molecules and 88% of these were used in the racemic form.⁸ When a drug is sold as a racemate it is believed that one enantiomer is active while the other is silent or has little activity. However, this is not always the case. The “silent” enantiomer some drugs can have undesired side effects. One such example is ketamine (Figure I.3).⁸

Ketamine is administered for anesthetic and analgesic purposes. Though *S*-(+)-ketamine has the desired anesthetic affect, *R*-(-)-ketamine causes hallucinations, restlessness and agitation of the patient after surgery. In this case, and many others, it would have been beneficial to have identified and administered only the active enantiomer.⁸ This is only one of number of different cases where enantiomers of a single drug can have drastically different effects.⁹ Unfortunately, determination of absolute stereochemistry remains a difficult task for both academic and industrial chemists.

I.2: Conventional Methods for the Determination of Absolute Stereochemistry

X-ray crystallography, NMR derivatization, optical rotation (OR), optical rotatory dispersion (ORD), vibrational circular dichroism (VCD), electronic circular dichroism (ECD) and a sub-discipline of ECD, exciton coupled circular dichroism (ECCD) are the most commonly used methods for the determination of absolute configuration.^{10,11}

I.2.1: X-Ray Crystallography

X-ray crystallography subjects a crystalline solid to a beam of X-rays that diffract off the molecule in a unique pattern for each unique molecule. The diffraction pattern is then used to ascertain the three dimensional arrangement of the molecule. In the past, only assignment of relative stereochemistry could be achieved unless the molecule contained a heavy atom.¹²⁻¹⁴ However, new methods are emerging that bypass this requirement.¹⁵ Crystallographic techniques are the least ambiguous of all the methods listed above, however, the use of this method is limited by the necessity of a single crystal of high quality which is often a meticulous task if even possible.¹² However, a 2013 report in Nature by Fujita and co-workers demonstrated that the structure and absolute configuration of non-crystalline substrates could be determined by crystallographic techniques when the substrate was absorbed into a crystalline metal-organic framework.¹⁶

I.2.2: NMR Analysis

Perhaps the most widely used method for the determination of absolute stereochemistry utilizes NMR spectroscopy. Enantiomers of a molecule will provide identical

NMR spectra however, slight differences in NMR chemical shifts are observed when comparing diastereomers of a given molecule. With this in mind, Mosher and co-workers developed chiral derivatizing agents that would transform a enantiomeric pair into a set of diastereomers that could then be distinguished via NMR.^{17,18} Since Mosher, many groups have set out to improve upon the methodology. Two of the commonly used derivatizing agents are methoxyphenylacetic acid (MPA) and 9-anthrylmethoxyacetic acid (9-AMA), shown in Figure I.4 A.¹⁹⁻²² A recurrent element of all Mosher type derivatizing agents is the aromatic ring. Consider the example below: a chiral amine of unknown stereochemistry is derivatized with MPA.²³ The most favored conformation of the resulting amide is that in which the carbonyl of the amide and the hydrogens of both chiral centers lie in the same plane. As a result, the phenyl ring of the diastereomers will reside on opposite sides of the molecule. With the example above, when the *S* derivatizing agent is used the phenyl is oriented such that it shields the protons on R₁ causing an upfield shift of the NMR signal. Alternatively, when the *R* reagent is used the phenyl is oriented such that it shields the protons of R₂ thus shifting these protons upfield in the NMR spectrum. Being that the chirality of the derivatizing agent is known and with the assumption that the amide backbone is as described, the location of R₁ and R₂ is determined by the chemical shift differences ($\Delta\delta$ s) as observed in the NMR spectra. If the amine was of the opposite configuration, the observed $\Delta\delta$ s would be the opposite thus, the location of R₁ and R₂ would be switched.

A few key limitations of this methodology should be discussed. First, this method is limited by the substrate scope which initially included primary and secondary alcohols, primary amines and carboxylic acids.^{20,23,24} However, more recently, Mosher type derivatizing

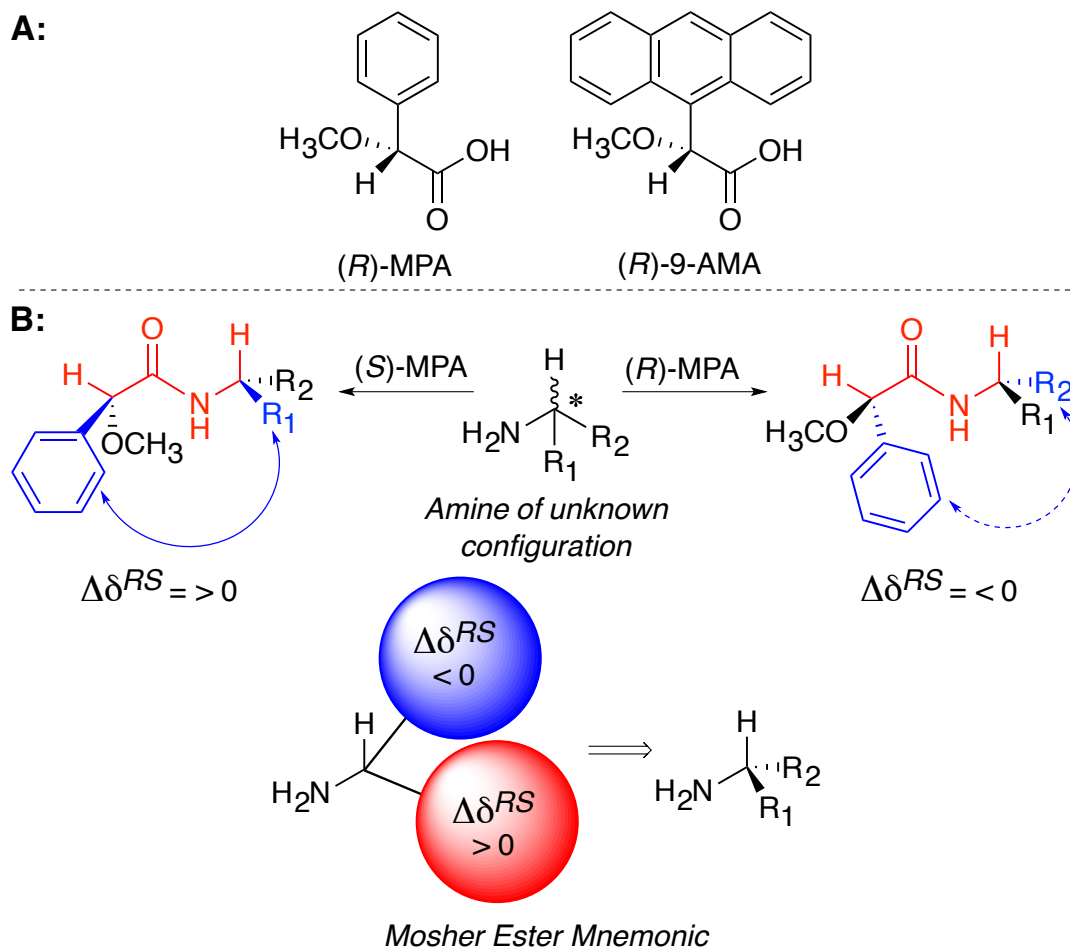


Figure I.4: **A:** Methoxyphenylacetic acid (MPA) and 9-anthrylmethoxyacetic acid (9-AMA) as representative examples of Mosher type derivatizing agents used in NMR determination of absolute stereochemistry. **B:** The mnemonic developed to correlate NMR chemical shifts of the diastereomeric pair back to the point chirality of the molecule of interest.²⁰

reagents have been used to conclusively assign the configuration of cyanohydrins^{22,25,26} and thiols.²⁷ It is important to note that the choice of reagent can be a challenge.²⁸⁻³⁰ If the Mosher reagent is poorly chosen, the diastereomers could be indistinguishable, meaning the derivatization and analysis must be repeated with a different Mosher reagent expending

additional substrate and time. Finally, there is an inherent necessity for millimolar quantities of the substrate to complete the chemical transformation and the NMR analysis, which may not be practical.

I.2.3: Introduction to the Chiroptical Methods of Optical Rotation (OR) and Circular Dichroism (CD)

The spectroscopic methods of optical rotation (OR) or optical rotatory dispersion (ORD) and circular dichroism (CD) all have common roots, specifically, the interaction of plane or linearly polarized light with a chiral molecule. In brief, all electromagnetic radiation consists of two components, a magnetic field and an electric field (B and E respectively, Figure I.5). The two fields oscillate perpendicular to one another in the direction of the propagation of the beam of radiation. Light, as it leaves a source, travels along every possible electric field vector. Linearly polarized light (LPL) is the consequence of the source light passing through a polarizing filter that only allows light of a specific electric field vector to proceed to the sample chamber.

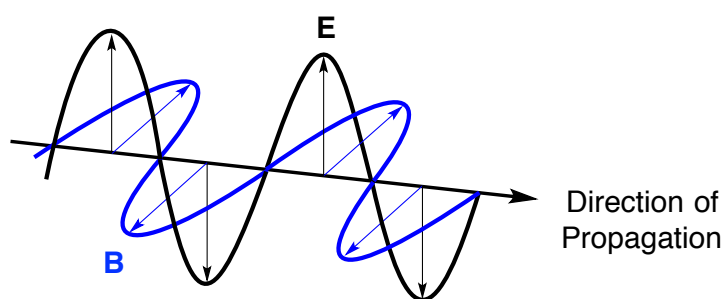


Figure I.5: A beam of electromagnetic radiation is comprised of an electric field (E, black) and a magnetic field (B, blue) perpendicular to one another traveling along the propagation vector.

This LPL is composed of two components, namely, right circularly polarized light (RCPL) and left circularly polarized light (LCPL, Figure I.6 A). These are so named because the electric field vector rotates around the propagation axis causing the radiation follow a clockwise (RCPL) or counterclockwise (LCPL) helix as the beam of radiation propagates (Figure 1.6 B). The vector addition of these two circularly polarized beams results in the LPL and the relative phase of the two circularly polarized beams determines the plane for the LPL. As this linearly polarized light passes through a chiral substrate, the three dimensional arrangement of the molecule has several effects on the circularly polarized components. The speed at which the right and left

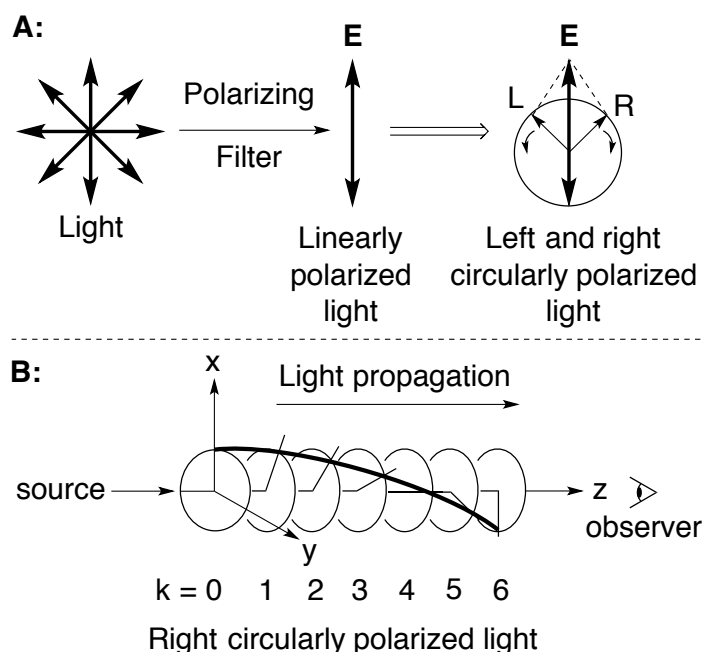


Figure I.6: **A:** The light from a source is unpolarized, traveling along all possible vectors. A polarizing filter isolates light of a single linear vector thus generating linearly polarized light. This linearly polarized light is the mathematical result of vector addition of a right (RCPL) and left circularly polarized light (LPCL). **B:** As RCPL propagates it follows a right or handed helix.

circularly polarized beams propagate will be different, $c_L \neq c_R$, which in turn causes $\lambda_L \neq \lambda_R$. Also, the extent to which the two components are absorbed will be different, $A_L \neq A_R$, thus $\epsilon_L \neq \epsilon_R$. These differences are the basis for optical rotation and circular dichroism.³¹

Optical rotation measures the rotation of the plane of the linearly polarized light after passing through a chiral medium. The rotation is a result of the circularly polarized beams traveling at different speeds after interaction with the molecule which changes the relative phase of the two circularly polarized beams. Vector addition of the beams after interaction will generate linearly polarized light in a different plane than the initial beam (Figure I.7). Optical rotation (OR or α) is the measurement of this rotation at a single wavelength; commonly at the sodium D-line (α_D). Optical rotatory dispersion (ORD) is the measurement of the optical rotation values over a range of wavelengths. By convention, a positive optical rotation is reported if the rotation occurs in a clockwise fashion and a negative value for a counterclockwise rotation. A related value, specific rotation ($[\alpha]$), is the optical rotation of a

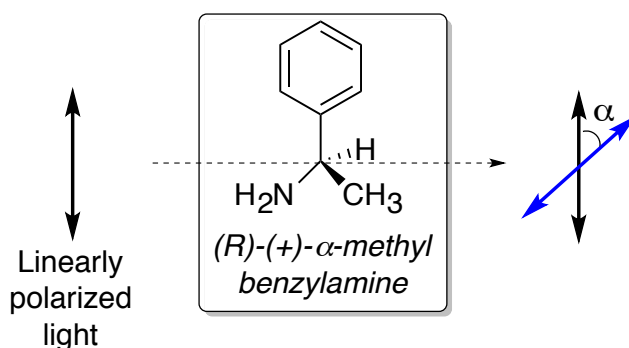


Figure I.7: An illustrative example of optical rotation with *(R)*-(+)- α -methylbenzylamine.

As the beam of linearly polarized light (bold black arrow) passes through the chiral amine, the plane is rotated α degrees clockwise (resulting beam as bold blue arrow).

This substrate has a positive optical rotation.

given sample with concentrations of grams per 1 milliliter for a pure liquid compound or grams per 100 milliliters for a solution, measured in a cuvet with a path length of 1 decimeter.³¹

Optical rotation aids in the assignment of configuration in that, enantiomers of any given chiral molecule will provide optical rotations of equal magnitude but opposite sign (For an example of ORD see Figure I.11, green line³²).³³ Unfortunately, there is no simple method to correlate the sign of an optical rotation to the absolute configuration of the molecule. Thus, this method is empirical. To conclusively assign the absolute stereochemistry of an unknown molecule, optical rotation must be used in combination with another method of assignment including but not limited to XRD, NMR analysis or chemical transformation to a molecule of known configuration and optical rotation.^{33,34} However, with the development of more sophisticated computational programs, the optical rotation for enantiomeric pairs of a molecule can be predicted. By comparison of the theoretical and experimental values, the absolute configuration can be assigned.³⁵⁻³⁸

Circular dichroism (CD), first discovered in the 1890s by Amié Cotton, is a measure of the difference in molar absorptivity ($\Delta\epsilon$, Equation I.1) for LCPL and RCPL when interacting with a

$$\Delta\epsilon \equiv \epsilon_L - \epsilon_R \quad (\text{I.1})$$

chiral molecule. Practically speaking, the epsilon values cannot be directly measured. Instead, the difference in absorbance (ΔA) for the right and left-circularly polarized beams is determined. Then using the Beer-Lambert-Bouguer Law the value of ΔA is converted into $\Delta\epsilon$. Beer's Law (Equation I.2) states that absorbance (A) is equal to the ratio of the intensity of the

$$A = \log_{10} \frac{I_0}{I} = \epsilon cl \quad (\text{I.2})$$

light prior to interaction with the sample (I_0) and the intensity light after passing through the sample (I). It also states that absorbance is the product of the extinction coefficient (ϵ), concentration of the sample (c , in moles per liter) and the path length of the cuvet (l , in centimeters). For CD purposes, the absorbance of the right (A_R) and left (A_L) circularly polarized beams are measured separately and the difference in absorbance are used to determine first ΔA (Equation I.3) then $\Delta \epsilon$ (Equation I.4), assume that $I_{0R} = I_{0L} = I_0$.³¹

$$A = A_L - A_R = \log_{10} \frac{I_{0L}}{I_L} - \log_{10} \frac{I_{0R}}{I_R} = \log_{10} \frac{I_R}{I_L} \quad (I.3)$$

$$\Delta \epsilon = \frac{1}{cl} \Delta A \quad (I.4)$$

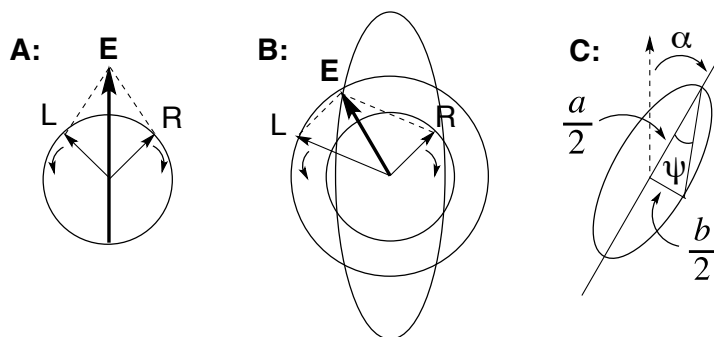


Figure I.8: **A:** Linearly polarized light, prior to interaction with a chiral substrate, is comprised of right and left circularly polarized light with equal, intensity and speed. **B:** After interaction with a chiral substrate, the intensities of the circularly polarized beams will be different as a result of one being absorbed more. As a result, the linearly polarized light will be elliptical. **C:** The linearly polarized light after interaction with a chiral substrate taking into account the rotation of the plane due to the difference in speeds of propagation.³¹

The initial circularly polarized beams are equal ($I_{OR} = I_{OL}$, Figure I.8 A), but after interaction with the chiral substrate the two are no longer equal ($I_L \neq I_R$). The vector sum of the two circularly polarized components creates a resultant linearly polarized beam that follows an elliptical path (Figure I.8 B). As discussed above, the speeds of propagation is also different, which causes a rotation of the plane of the resultant linearly polarized light by a certain degree (α , Figure I.8 C). Although not common, the molar ellipticity, which is calculated from ψ , has been reported for chiral molecules.³¹

To understand why the extinction coefficients of LCPL and RCPL are different, one must consider the underlying processes involved when a molecule absorbs light. Absorption of electromagnetic radiation, promotes an electron from the ground state to an excited state. This movement of negative charge momentarily creates a dipole called the electric transition dipole moment (etdm). For a chiral molecule, this excited electron can relax in a helical manner. The helical redistribution of a charge momentarily creates a magnetic transition dipole

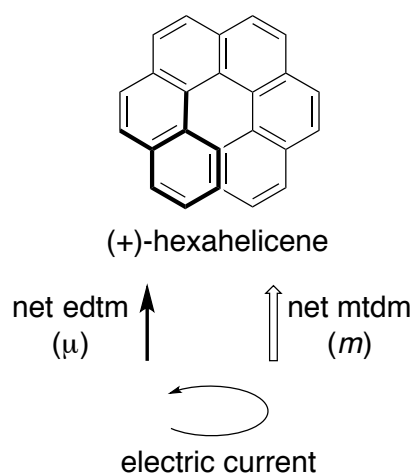


Figure I.9: Relaxation of an electron in (+)-hexahelicene creates an electronic, a magnetic transition dipole moment and an electric current.

moment (mtdm) and a circular electric current. Consider (+)-hexahelicene (Figure I.9), when a photon of radiation is absorbed the etdm and the mtdm are generated as indicated by μ and m , respectively.³⁹ The rotation of the charge, the circular electric current, is determined by using the “right hand rule” which states that the outstretched thumb of the right hand defines the direction of the magnetic transition dipole moment when the fingers are curved along the path of the electric current. For this example, the electric current will follow a left-handed helix. This electric current interacts differently with the LCPL than the RCPL thus creating the difference in molar absorptivity coefficients and circular dichroism.³¹

Typically the value of $\Delta\epsilon$ is reported by the instrument and in honor of Amié Cotton, the signal observed is called a Cotton effect. For any given molecule, Cotton effects are observed at approximately the same wavelengths as the molecule would absorb radiation in infrared (IR) or UV-Vis spectroscopy. Vibrational circular dichroism (VCD) measures this difference in molar absorptivity in the IR wavelengths and electronic circular dichroism (ECD) is measured in the UV-Vis wavelengths. Therefore, VCD is more general as most molecules absorb IR radiation but, ECD is limited to molecules containing a UV-Vis active chromophore. Unlike IR or UV-Vis, where absorption of radiation is manifested as a signal with a positive amplitude, in CD, the

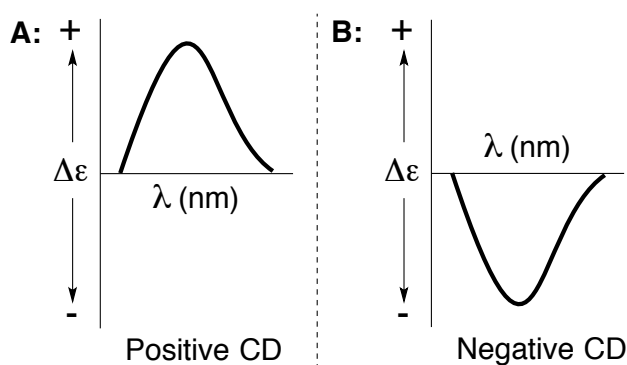


Figure I.10: A: Positive and B: negative CD curves or Cotton effects.

differential absorption of circularly polarized light results in a Cotton effect of either a positive or negative amplitude (Figure I.10). Rotational strength, R , describes the sign and the

$$R = \mu \cdot m = |\mu||m| \cos\beta \quad (I.5)$$

magnitude of a Cotton effect. This value is the scalar product of the etdm (μ) and mtdm (m) where β is the angle between the dipole moments (Equation I.5). The Cotton effect is positive when β is an acute angle or when the dipole moments are parallel ($0^\circ \leq \beta < 90^\circ$) and negative when β is an obtuse angle or when the dipole moments are antiparallel ($90^\circ < \beta \leq 180^\circ$). When $\beta = 90^\circ$, the value of cosine is zero thus, R is zero. When considering (+)-hexahelicene (Figure I. 9), the etdm and mtdm are parallel to one another ($\beta = 0^\circ$) thus a positive Cotton effect is predicted and observed.³¹

Similar to optical rotation, enantiomers of a molecule provide CD spectra with signals of equal amplitudes but opposite sign (Figure I.11, red line³²). CD also suffers the limitations of optical rotation in that, CD is an empirical method of assigning configuration thus, a theoretically calculated spectra is necessary for comparison to assign absolute stereochemistry.⁴⁰⁻⁴⁶ In addition, it has been shown that even with high level calculations, the calculated spectrum can predict the wrong sign which would lead to incorrect assignment of absolute stereochemistry.^{37,38,47-50}

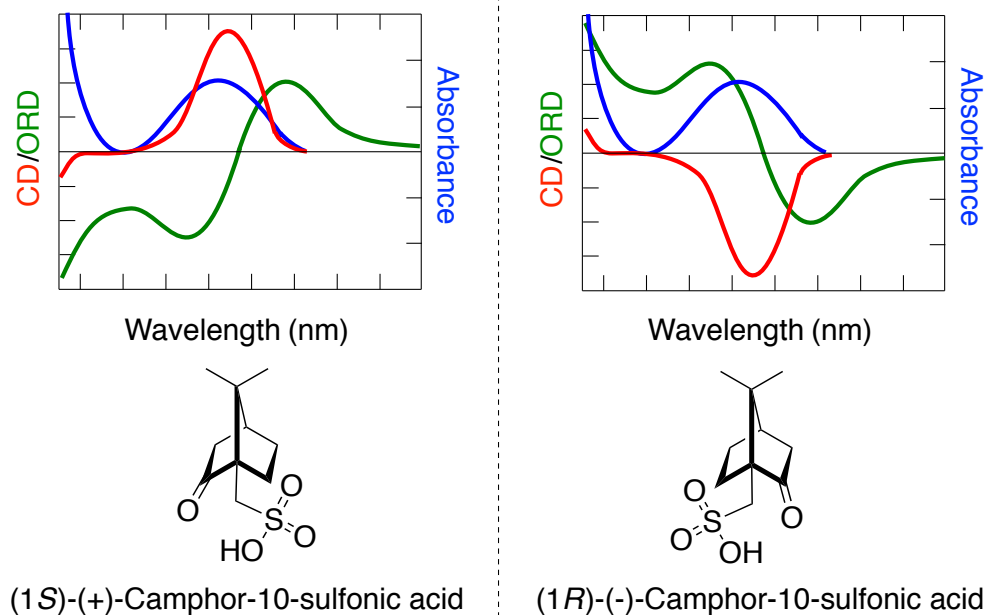


Figure I.11: The absorbance (blue lines), ORD (green lines) and ECD (red lines) of the enantiomers of Camphor-10-sulphonic acid. Note that the absorbance spectra are identical but the ORD and ECD are of opposite signs.³²

As for the instrumentation, Figure I.12 is an illustration of the interior of our CD spectropolarimeter.⁵¹ As discussed above, CD is the difference in absorption of LCPL and RCPL by a chiral substrate thus, the instrument must generate and detect the circularly polarized light. Within the instrument, the non-polarized source light, typically from a high energy xenon arc lamp, is focused by mirrors, M_1 and M_0 , passing through slit 1 (S_1) to enter the instrument. A series of mirrors ($M_2 - M_5$), prisms (P_1 and P_2) and slits ($S_1 - S_3$) generate the linearly polarized light. The prisms have different axial orientations, the first is horizontal and the second is vertical, which generates monochromated linearly polarized light. Once through slit 3, the linearly polarized light passes through a lens (L), a filter (F) then, a piezoelastic modulator (CDM).

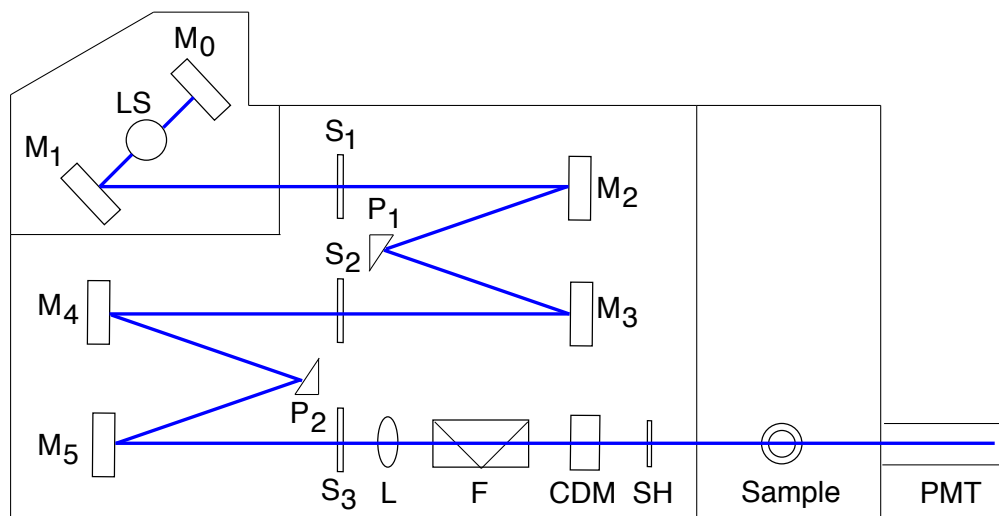


Figure I.12: A schematic representation of the JASCO J-810 CD spectrophotometer. LS: Light Source, M₀ - M₅: Mirrors, S₁ - S₃: Slits, P₁ (horizontal optical axis) and P₂ (vertical optical axis): Prisms, L: Lens, F: Filter, CDM: Modulator, SH: Shutter, PMT: Photomultiplier Tube.⁵¹

The piezoelectric modulator is a quarter wave plate, composed of a quartz (fused silica) crystal and a piezoelectric element. When the piezoelectric element is oscillating, typically at 50 kHz, the quartz crystal is mechanically compressed and stretched. This mechanical stress causes the quartz to exhibit birefringence or the ability split a beam of radiation into two different polarization components. The piezoelectric modulator is aligned such that the vector of the LPL is off set from the axis of the crystal by 45° (Figure I.13 A). Prior to interaction with the modulator, the two electric field components of the LPL, RCPL and LCPL, are in phase with one another. The 45° rotation of the LPL to the axis of the crystal ensures that the horizontal electric field component, E_y or LCPL, is aligned with the axis of the crystal. The other electric field component of the LPL, E_x or RCPL, is perpendicular to the axis of the crystal. When the modulator is not under stress, the two electric field components will remain in phase after

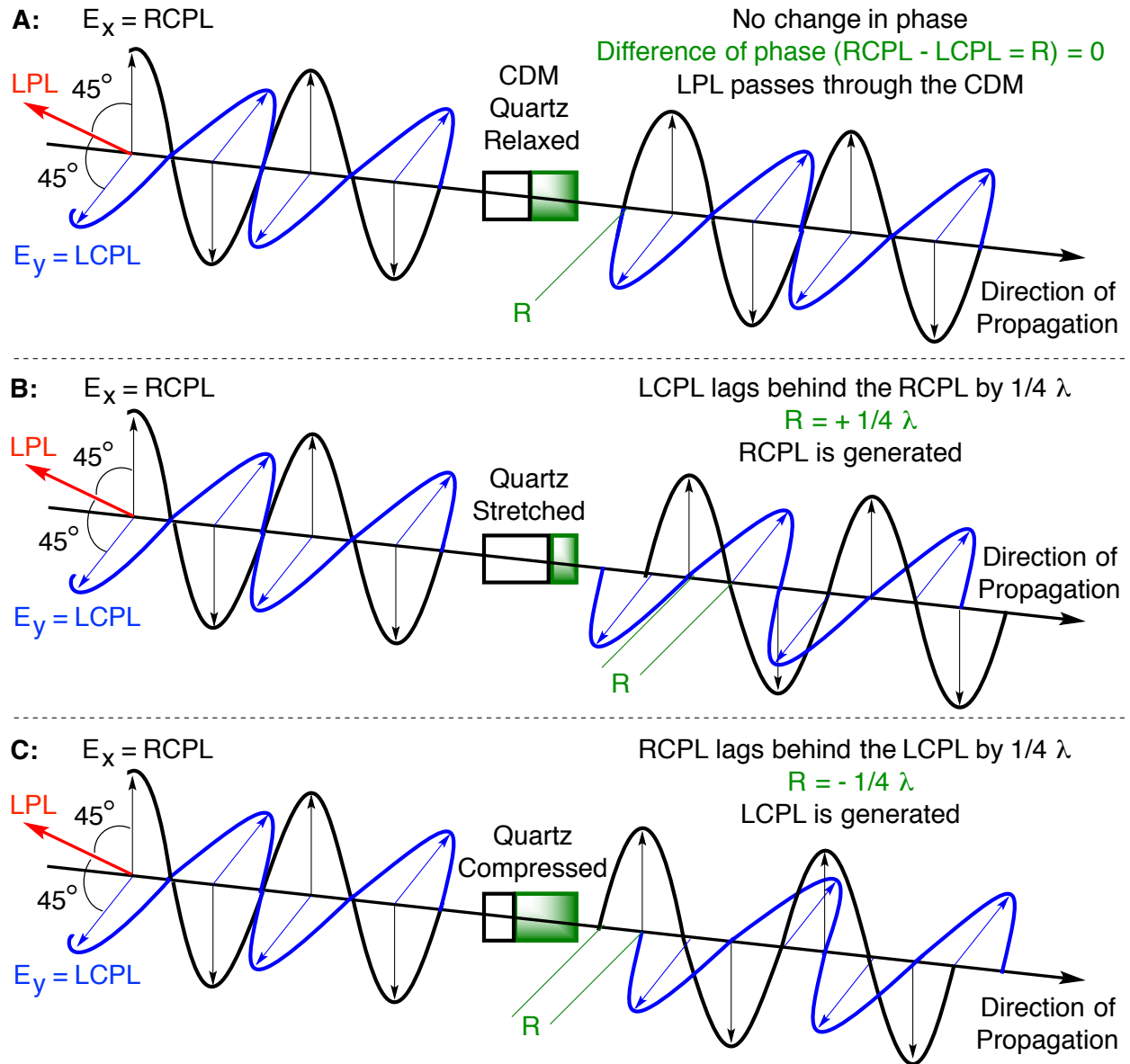


Figure I.13: The affect of the CDM on LPL. See text for the full description. **A:** When the quartz is relaxed, linearly polarized light passes through the modulator. **B:** Stretching the quartz results in RCPL and **C:** Compressing the quartz generates LCPL.

interaction with the crystal (Figure I.13 A) and the LPL passes through the crystal unchanged. However, when the linearly polarized light is passed through the quartz under mechanical stress, the electric field components will no longer be in phase with one another and circularly

polarized light is generated. In other words, when the RCPL and LCPL vectors are in phase the vector addition results in LPL. After interaction with the birefringent quartz, the RCPL and LCPL are no longer in phase and the vector addition leads to either RCPL or LCPL.

The type of mechanical stress, compression or stretching, will determine the type of circularly polarized light that is generated. Stretching of the crystal, as in Figure I.13 B, causes the horizontal electric field component, LCPL to lag behind the vertical electric field component, RCPL. When the crystal is at the maximum stretch, the LCPL lags behind the RCPL by one-quarter wavelength or these components are out of phase by one-quarter wavelength, which is defined as $+1/4 \lambda$. The vector addition of the two components results in RCPL. Alternatively, when the crystal is compressed, the horizontal electric field component comes ahead of the vertical component or the RCPL component lags behind the LCPL (Figure I.13 C). When the crystal is at maximum compression, the RCPL lags behind the LCPL by one-quarter wavelength therefore these are out of phase $-1/4 \lambda$ and the vector addition of the electric field components results in LCPL. The crystal is not always relaxed or at maximum compression or stretch, so, at the points in between, either right-handed or left-handed elliptically polarized light is generated. Figure I.14 is a graphical representation of the polarization of the light passing through the modulator during a full oscillation of the quartz crystal.

The circularly polarized light, alternating between RCPL and LCPL as generated by the CDM, enters the sample chamber. The circularly polarized light then passes through the sample and what is transmitted through the sample is detected by a photomultiplier tube (PMT) by creating a current that is proportional to the number of photons that enter the PMT. A two separate signals are generated; one for each of the circularly polarized beams. Finally, the

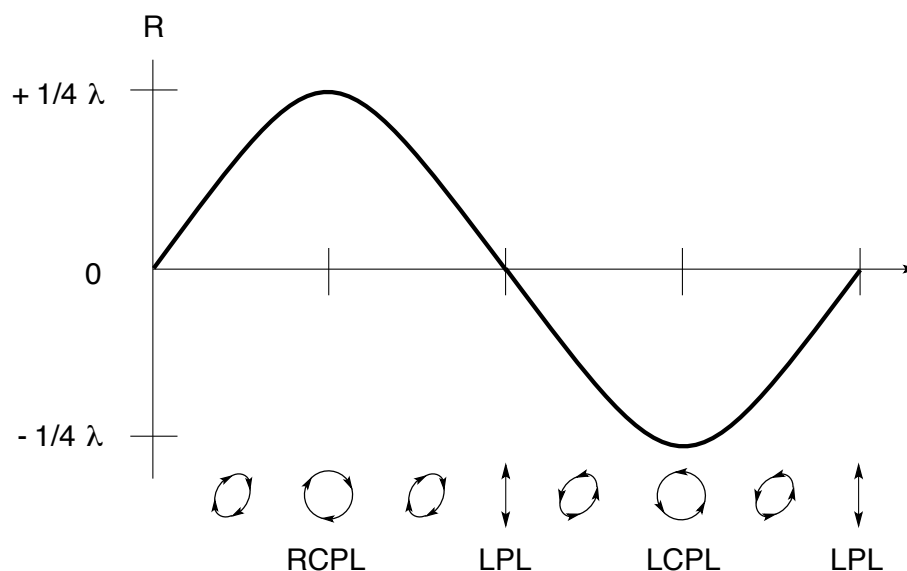


Figure I.14: Graphical representation of the polarization for the linearly polarized light passing through the CDM. A full oscillation of the quartz is represented. RCPL and LCPL are generated at the apexes and LPL when the quartz is relaxed. At all points in between, elliptically polarized light is emitted.

generated signals are recorded by the lock-in amplifier then the signal is transferred to the software. The software converts the intensity of the signal from the PMT into absorption then, subtracting the absorption of the two circular polarized beams provides the CD spectrum which is displayed for the user.

I.3: Introduction to Exciton Coupled Circular Dichroism (ECCD)

I.3.1: Theoretical Background of ECCD

Exciton coupled circular dichroism (ECCD), a sub-discipline of ECD, was pioneered by Harada and Nakanishi and is summarized as the following.^{31,52} The phenomena of ECCD is observed when a chromophore containing molecule exhibits differential absorption of circularly

polarized light within the UV-Vis wavelengths. However, for a molecule to be ECCD active, it must contain two or more independent chromophores that are close in space and oriented in a helical fashion relative to one another. The underlying physical principals of ECCD are similar to ECD in that, absorption of electromagnetic radiation promotes an electron of the chromophore to an excited state creating an electric transition dipole moment (etdm) and a magnetic transition dipole moment (mtdm). ECCD occurs when the chromophores are close enough in space to allow these transition dipole moments to interact. Consider an example of a molecule with two chromophores (i and j). Upon absorption of light each of the chromophores present will enter an excited state. If close in space, the excited states of i and j can couple to create two new energy states. The α state has lower energy than the excitons before coupling and the β state is of higher energy than the excitons before coupling (Figure I.15). The difference in

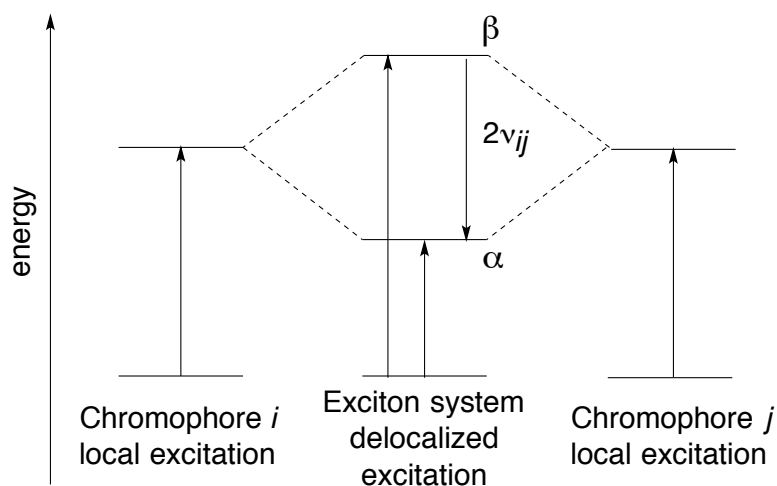


Figure I.15: Energy level diagram for exciton coupled circular dichroism. When in the excited states, the chromophores i and j will couple creating two new energy states, one with lower energy (α) and one with higher energy (β) than the excited state of the isolated chromophore.⁵²

energy between the α and β states is called the Davydov splitting and is denoted as $2\nu_{ij}$.

The energies of the α and β states are a consequence of the in-phase (symmetric) and out-of-phase (anti-symmetric) coupling of the etdms of the two chromophores. For both UV-Vis and ECCD spectroscopy, a set of peaks would be expected, as the different energies of these states would cause absorption at different wavelengths with the higher energy β state absorption being blue shifted in comparison to the lower energy α state. The Davydov splitting would appear as the difference between the $\lambda_{\max}$ of the two absorptions. In practice though, the Davydov splitting is typically far too small for the peaks to be resolved in UV-Vis and a single absorption band is observed (Figure I.16A). However, in ECCD, the in-phase and out-of-phase coupling of the etdms causes the corresponding Cotton effects to have opposite signs. Therefore, the two absorptions resolve into the bisignate curve that is characteristic of ECCD (Figure I.16 B).

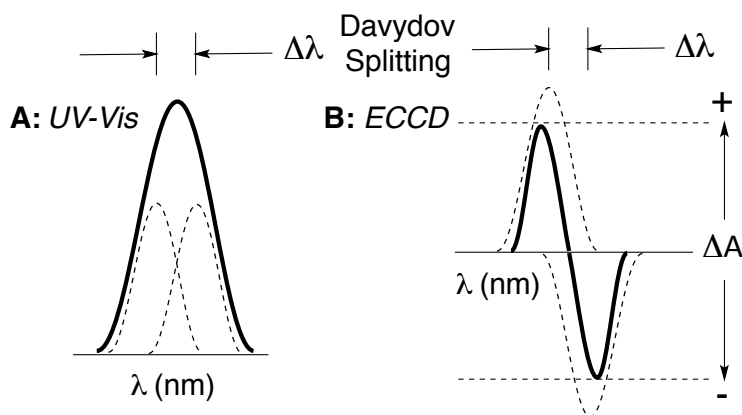


Figure I.16: A: UV-Vis spectrum and **B:** ECCD spectrum of two degenerate chromophores interacting through space. The dashed lines represent the hypothetical absorptions of the two energy states. The solid lines are the observed summation spectra.⁵²

As with ECD, rotational strength, R , is a representation of the amplitude and the sign of ECCD signal. However, for ECCD, additional factors must be considered. The sign of the Cotton effects are a result of the in-phase (symmetric) or out-of-phase coupling (asymmetric) of the chromophores. Again, for simplicity, consider an ECCD active system with two interacting chromophores, for example the dibenzoate of a steroidal diol (Figure I.17 A). Each of the chromophores has an independent etdm, as indicated by the arrows through the benzoate. There are four possible combinations for coupling of these dipoles. In two cases, the dipoles

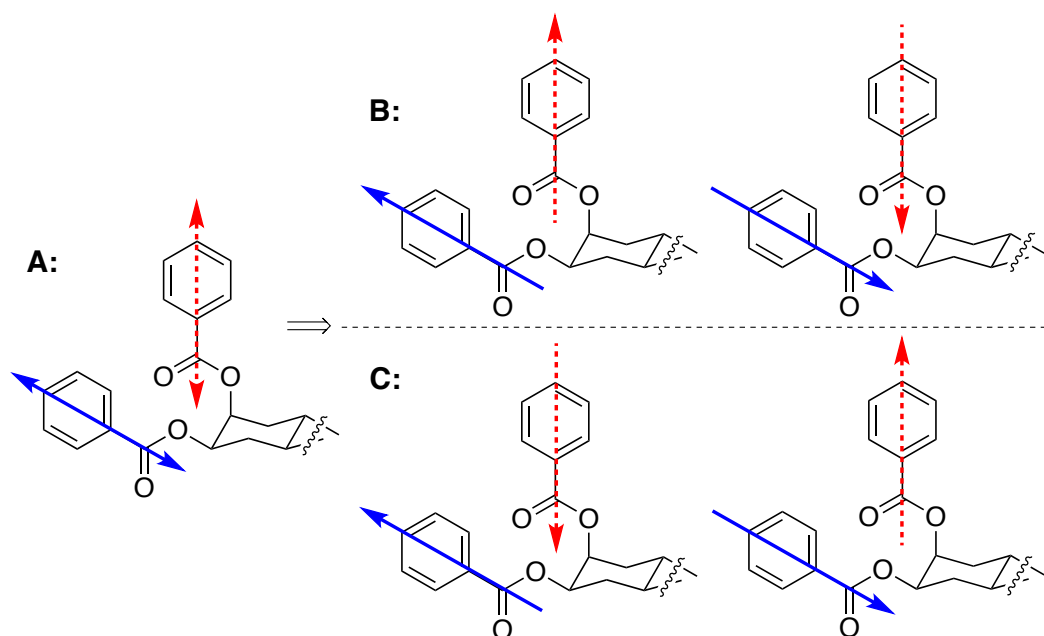


Figure I.17: A dibenzoate of a steroidal-1,2-diol as an illustrative example of the coupling of the electric transition dipole moments. **A:** Each benzoate has an independent etdm as indicated by the blue and red arrows. The solid and dashed arrows indicate front and back, respectively. There are four possible coupling modes of the two independent etdms. **B:** Two are in-phase or symmetric and **C:** two are out-of-phase or asymmetric.

are coupled symmetrically (Figure I.17 B) and two cases where the dipoles are coupled asymmetrically (Figure I.17 C). For the symmetrically coupled dipoles, the net etdm from the coupled system lies along the chromophoric C2 axis. The asymmetrically coupled system has a net etdm that will lie perpendicular to the chromophoric C2 axis. Also, it is important to note that the symmetrically coupled systems are higher in energy due to dipole repulsion. For the purpose of visualization, if the partial etdms of the benzoate chromophores are placed in a cylinder that is aligned with the net etdm for the coupled system, the electrical current follows a helical path as indicated by the curved arrows (Figure I.18). The symmetric system has a

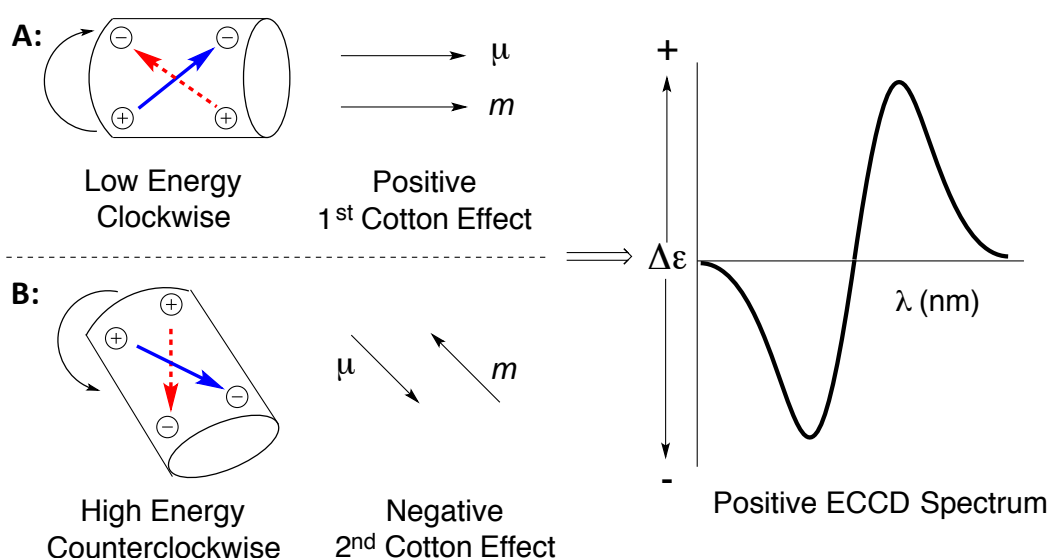


Figure I.18: The low (asymmetric) and high (symmetric) energy states for the dibenzoate presented in Figure I.17. The electric current and magnetic transition dipole moments generated for these state will correspond to a positive Cotton effect for the low energy state and negative Cotton effect for the high energy state. Overall a positive bisignate ECD signal is expected.

counterclockwise current and the asymmetric has a clockwise current. Being that the flow of the electric current is known, the right hand rule can then be used to determine the orientation of the magnetic transition dipole moment. In this case, the mtdm of the low energy state is parallel to the etdm and the mtdm of the high energy state is anti-parallel to the etdm. This provides Cotton effects that are positive and negative for the low and high energy states respectively. Again, the low energy state is red shifted by comparison to the high energy state therefore, a positive ECCD bisignate curve would be expected.

$$R_{\alpha\beta} = (\pm)\left(\frac{1}{2}\right)\Pi\sigma_0 R_{ij} \cdot (\vec{\mu}_{ioa} \times \vec{\mu}_{joa}) \quad (I.6)$$

The sign and amplitude or rotational strength, R , of the ECCD signal can be predicted by Equation I.6 where σ_0 is excitation number of transition from 0 to α state, R_{ij} is the distance between the chromophores and μ_{ioa} , μ_{joa} are the electric transition dipole moments. The

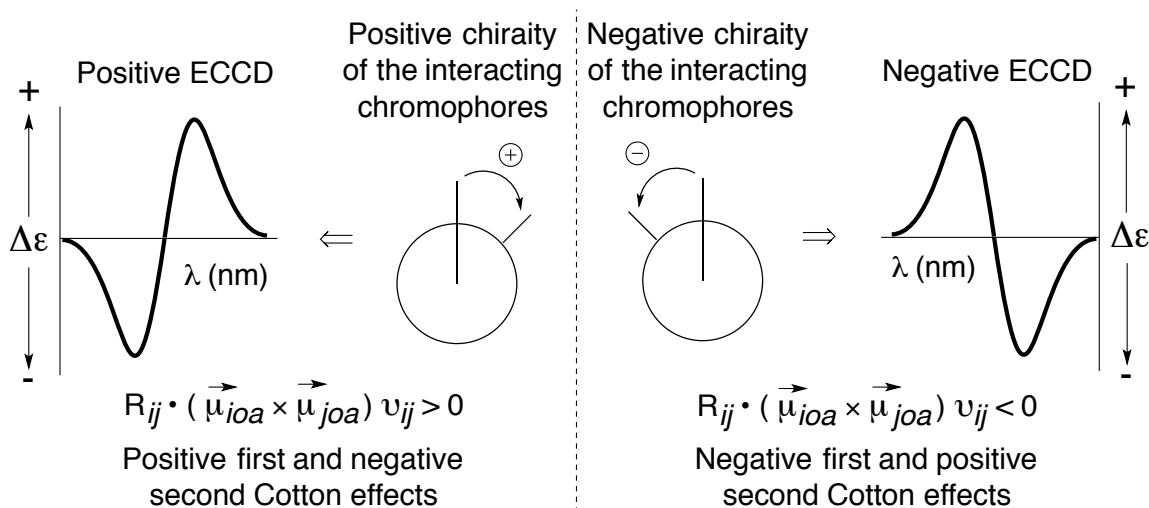


Figure I.19: Definition of exciton chirality for a binary system. The clockwise arrangement of chromophores will produce a positive signal and a negative signal for counterclockwise.⁵²

amplitude of R is essentially the product of the distance between the chromophores and the vector multiplication of the ϵ values of the chromophores. The sign of R , whether a positive or negative ECCD is observed, is determined by the arrangement of the ϵ values relative to one another (Figure I.19). When the chromophores are arranged in a clockwise fashion looking from the front chromophore to the back chromophore, R is positive so, the first Cotton effect observed will be positive and the second will be negative. The counterclockwise arrangement of chromophores provides a negative ECCD signal therefore, the first Cotton effect observed will be negative and the second will be positive. Therefore, the sign of an ECCD couplet can be correlated to the spatial arrangement of the coupling chromophores, which in turn can be used to determine absolute stereochemistry at the sites of the chromophores. In this manner, ECCD is a non-empirical tool for determining absolute stereochemistry.

I.3.2: Applications of ECCD for the Determination of Absolute Stereochemistry

As discussed above, ECCD results from the coupling of two or more chromophores that are close in space and oriented in a helical fashion. These chromophores can be inherent to the molecule or introduced by means of derivatization. Note that by convention, the measure of ECCD, amplitude (A), is the difference in $\Delta\epsilon$ of the first and second Cotton effects and indicates strength of the signal. If A is negative, the first Cotton effect is negative and the chromophores are arranged in a counterclockwise fashion. A positive A value indicates a clockwise arrangement of chromophores and the first Cotton effect is positive.

An early example of ECCD analysis to determine absolute configuration is that of (+)-*cis*-abscisic acid, a known plant-growth regulator. There was much debate over the configuration

of the lone hydroxyl chiral center (Figure I.20). In 1967, Cornforth and co-workers assigned the stereochemistry as *R* using a combination of CD and Mills' rules.^{53,54} However, in 1970, Burden and Taylor suggested that this assignment could be incorrect as abscisic acid and violaxanthin were shown to be related by chemical correlation and the configuration of violaxanthin had previously been determined as *S*.⁵⁵ In 1972, Isoe⁵⁶ and co-workers as well as Oritani and Yamashita⁵⁷ independently determined the configuration of abscisic acid to be *S* on the basis of correlations. By the end of 1972, Ryback, again using chemical correlations, this time with (*S*)-Malic acid, added to the argument by showing that the configuration of hydroxyl center is *S*.⁵⁸ In 1973, Nakanishi, et. al, contributed by the ECCD analysis of abscisic acid and an

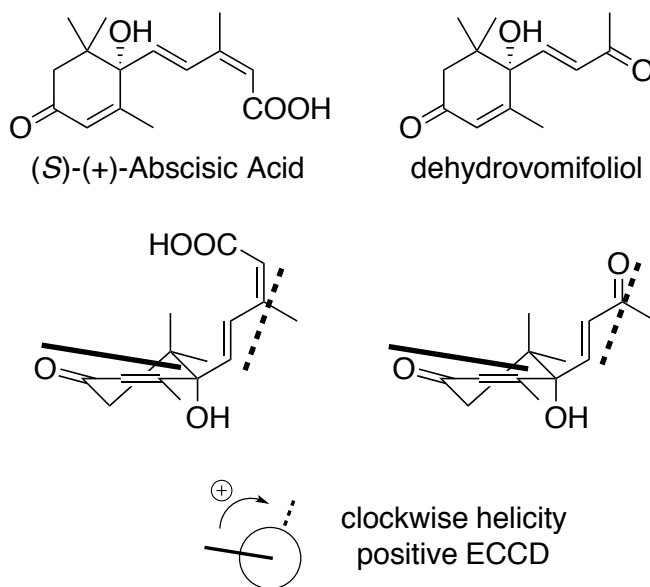


Figure I.20: The ECCD analysis of (*S*)-(+)-Absciscic acid and dehydrovomifoliol. The most stable conformation of each molecule is also shown. The double-headed arrows indicate the dipole moment of each chromophore with the bold arrow being in front and the dashed arrow in back. The chromophores are in a clockwise helical arrangement thus, a positive ECCD is expected and observed.⁶⁰

analog of known configuration, dehydrovomifoliol, for comparison. Both abscisic acid and dehydrovomifoliol have independent unsaturated carbonyl functionalities arranged in a clockwise helicity due to the hydroxyl center.^{59,60} Being that the configuration of dehydrovomifoliol was known, the observed positive ECCD couplet was expected. A positive ECCD couplet was also observed for abscisic acid thus, ECCD analysis confirmed that the hydroxyl configuration was correctly labeled *S*.

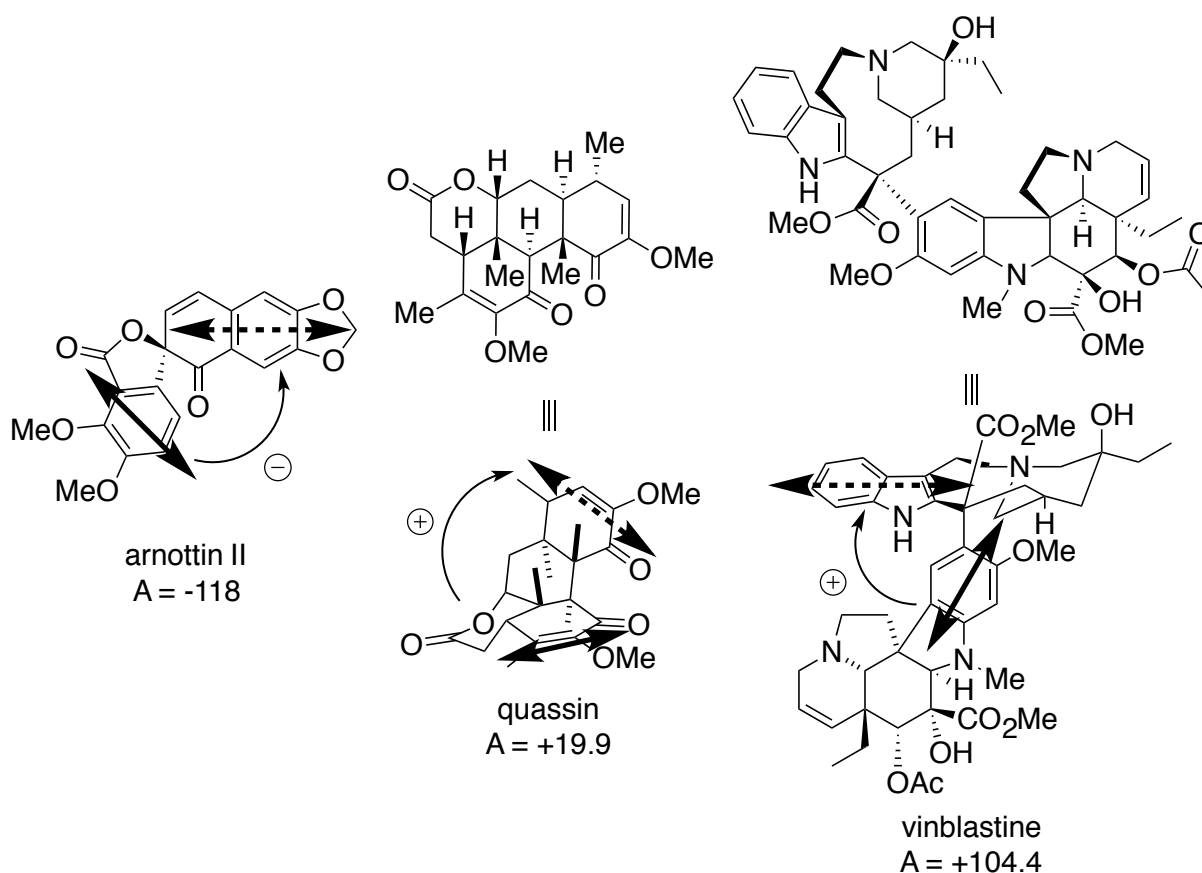


Figure I.21: ECCD of selected natural products. The dipole moments of the interacting chromophores are indicated by the double headed arrows. The curved arrows indicate the helicity between the chromophores. Arnottin II⁶¹ has a counterclockwise helix and a negative sign whereas quassin⁶² and vinblastine⁶³ have a clockwise helix and positive signs.

Since the 1970s, ECCD has been utilized for stereochemical determination of many other natural products containing chromophores such as, enones, dienes and aromatic heterocycles to name a few. The examples of arnottin II⁶¹, quassin⁶² and vinblastine⁶³ are shown in Figure I.21. For each, the dipole moments of the chromophores, the rational for the sign of the observed signal, and A of the observed signal are provided.

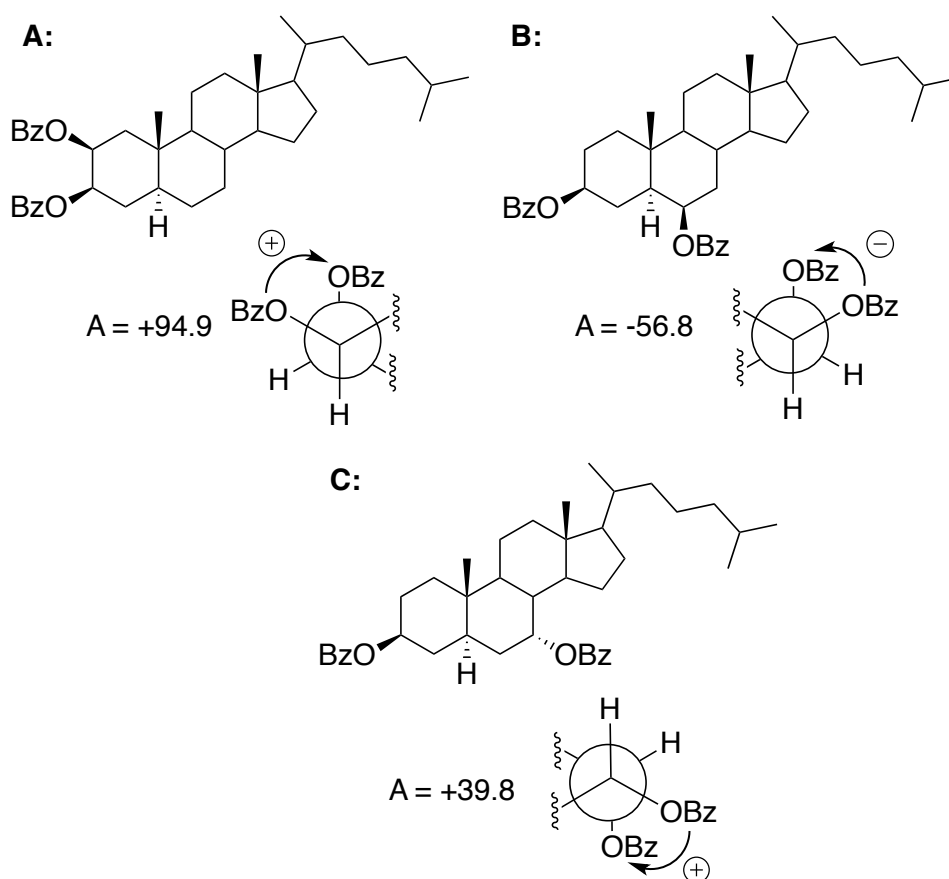
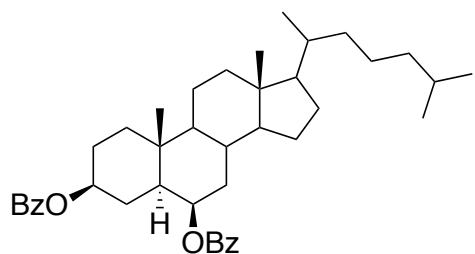


Figure I.22: Selected steroidal diols. With increasing distance, the ECCD amplitudes decrease. The Newman projections rationalize of the observed sign if only considering the carbons bearing the benzoates. Bz = *p*-(*N,N*-dimethyl)-aminobenzoate.⁵²

If a molecule does not inherently contain chromophores, derivatization of functional groups such as, alcohols or amines, can be the means to install the requisite chromophores. Steroids were extensively studied using the dibenzoate derivative method for ECCD. A series of steroidal diols were derivatized with varying benzoate groups to determine the effects of the extinction coefficient of the chromophore, distance and angle between the chromophores on the overall amplitude of the ECCD signal. Steroids were ideal for exploring these effects since they are rigid in conformation so location of the chromophore was not subject to conformational changes. Three important conclusions came from these studies. First, the amplitude of the ECCD signal is inversely proportional to the distance between the chromophores. Figure I.22 shows three diols derived from the steroid backbone where only the distance between the hydroxyl groups is significantly changed as the chromophore and the angle between the chromophores remains the same. The 1,2-diol (A) shows the largest ECCD amplitude and the 1,5-diol (C) shows the smallest ECCD amplitude.⁵²

Secondly, it was shown that chromophores with larger extinction coefficients produce larger amplitudes as the chromophore will have a larger etdm. Figure I.23 summarizes the



Bz	ϵ	Amplitude
<i>p</i> -NO ₂	15,100	-10.7
Ph	15,300	-15.5
<i>p</i> -OMe	20,400	-26.4
<i>p</i> -CN	24,600	-35.4
<i>p</i> -N(Me) ₂	30,400	-56.8

Figure I.23: The correlation of extinction coefficient (ϵ) with ECCD amplitude. As ϵ increases so do the ECCD amplitudes.⁵²

ECCD results for a series of 1,2-diols derivatized with various benzoate groups. In general, as the extinction coefficient increases so does the ECCD amplitude.⁵²

Finally, for vicinal diols, ECCD shows a dependence on the angle between the chromophores. The amplitude of the signal reaches a maximum when the chromophores are disposed at an angle of 70° . If the chromophores are at an angle of 0° or 180° , the ECCD amplitude is zero. Figure I.24 shows selected 1,2-diols and the observed ECCD signals. As expected, A, with an angle of 15° , produced the smallest amplitude and the angle of 105° produced the largest.⁵²

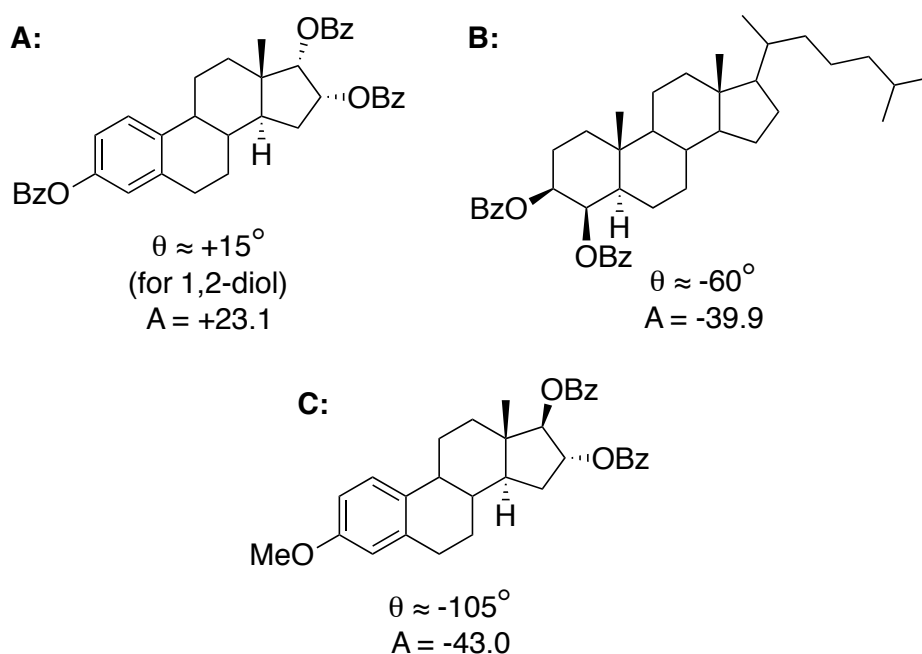


Figure I.24: ECCD amplitudes have an angular dependence. For these diols, only the angle between the benzoates changes significantly thus showing the change of ECCD amplitude based on the angle between the benzoates. Bz = *p*-chlorobenzoate.⁵²

The latter results encouraged the development of chromophores with larger extinction coefficients resulting in more intense ECCD signals. Additionally, an ECCD chromophore that has significantly red shifted λ_{max} in comparison to typical chromophores encountered in organic molecules (alkenes, ketones, aromatics, etc.) was highly desired. This would prevent the undesired coupling between the ECCD chromophores and any chromophores inherent to the organic molecule which complicates ECCD spectra as observed with the benzoate derivatives. In 1995, Nakanishi and co-workers derivatized a steroidal amino alcohol with 10,15,20-trisarylporphyrin-5-benzoic acid.⁶⁴ The triphenylporphyrin was known to have a large

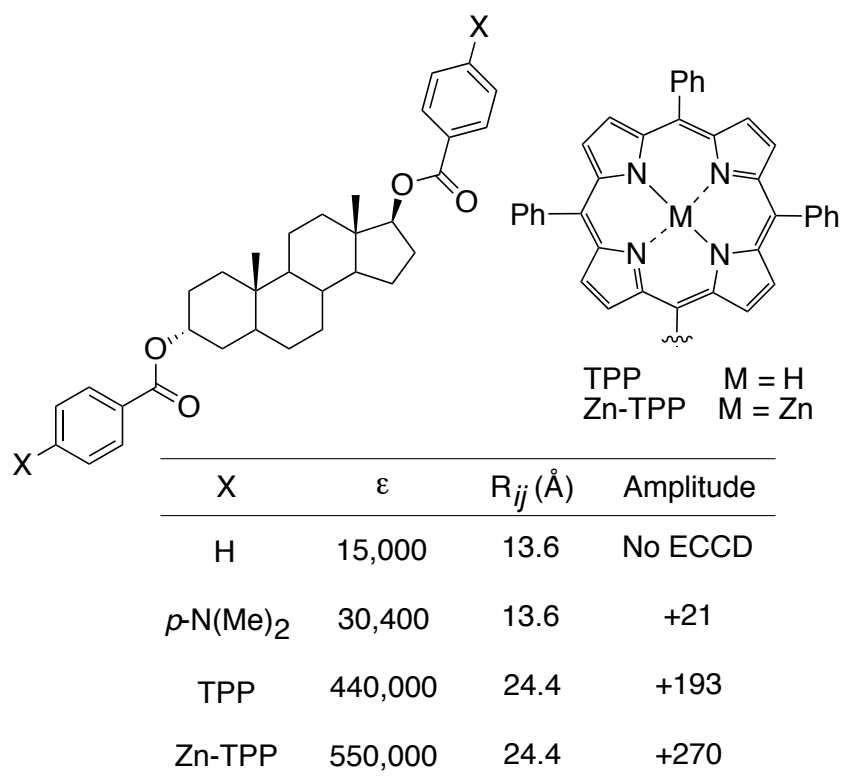


Figure I.25: Long distance benzoate coupling with a steroidal diol. Derivatization with porphyrin benzoates gives more intense ECCD couplings due to the large ϵ values. The distance between the chromophores (R_{ij}) is increases for the porphyrin benzoates due to the size of the porphyrin.⁵²

extinction coefficient ($440,000 \text{ L mol}^{-1} \text{ cm}^{-1}$) a $\lambda_{\text{max}} \sim 414 \text{ nm}$. Figure I.25 compares the original benzoate derivatives with the porphyrin derivatives. The porphyrin derivatives provide ECCD signals 10-fold larger than the benzoate precursors.

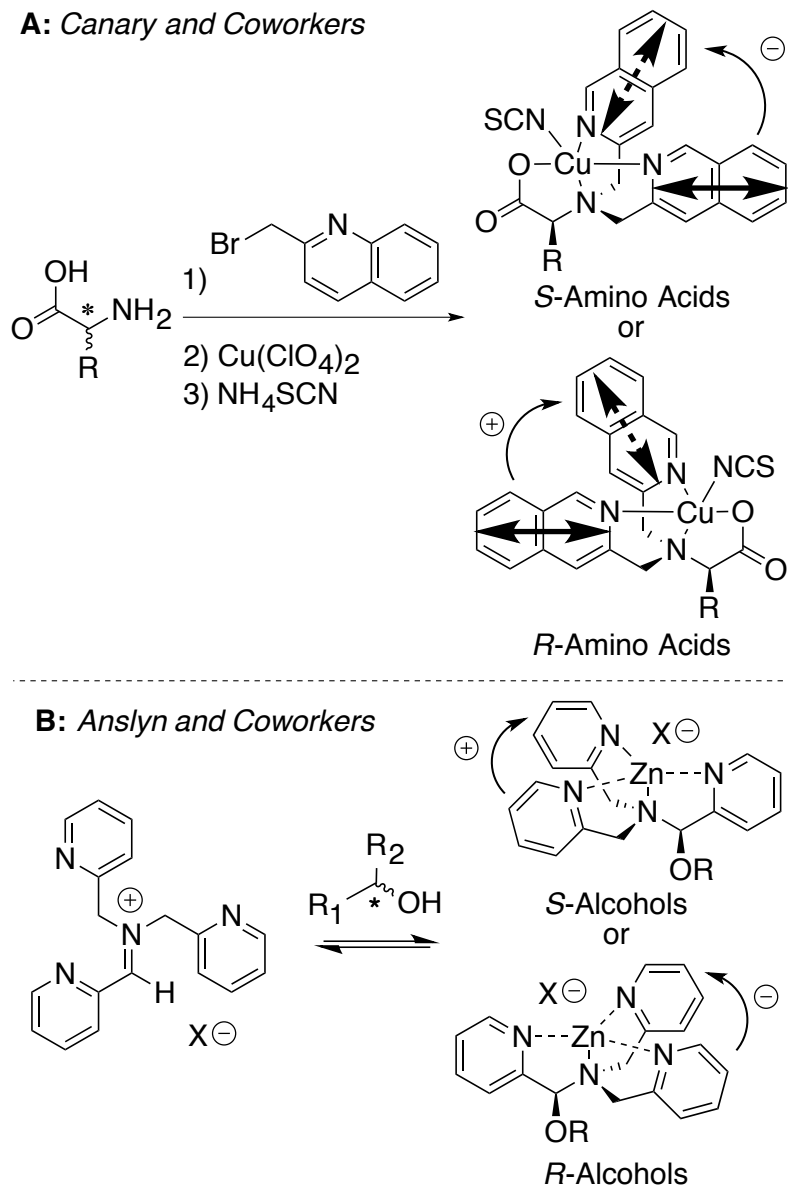


Figure I.26: Recently developed ECCD host-guest complexes. **A:** Canary's copper complex for amino alcohols^{65,66} and **B:** Anslyn's tripodal zinc complex for alcohols.^{72,73}

In more recent years, other groups have developed new derivatization techniques for ECCD applications. Canary and coworkers have shown that the configuration of amino acids can be determined by first derivatizing the amino group with quinoline groups (Figure I.26 A). Upon addition of copper II hypochlorite, a chiral complex forms causing the chromophores to be helically disposed. The sign of the observed ECCD signal can be directly correlated to the configuration of the amino acid.^{65,66} The authors have also reported the determination of configuration for amino acids with zinc tripods,^{67,68} use of the tripod for determination of configuration of amines⁶⁹ and a redox switchable copper tripod.^{70,71}

In 2012, Anslyn and coworkers optimized a one-pot multicomponent assembly of an ECCD active tripod (Figure I.26 B).^{72,73} In the presence of zinc II triflate, a chiral alcohol attacks the achiral iminium precursor forming the complex. The chirality of the alcohol dictates the facial selectivity upon addition to the iminium, which in turn, determines the helicity of the pyridine chromophores. The ECCD signal can be correlated to the configuration of the chiral alcohol.

The methods previously discussed require derivatization of the chiral molecule. In an effort to avoid chemical derivatization, Nakanishi and coworkers developed a metalloporphyrin tweezer (Figure I.27).⁷⁴ The tweezer is two metalloporphyrins, linked by a flexible alkyl chain that is capable of adopting a helicity depending on the chirality of the guest molecule coordinated to the porphyrin metal centers. Notable ECCD methodologies that utilize the porphyrin tweezer for the determination of absolute configuration have been developed by Nakanishi, Inoue and our lab. Selected examples will be discussed in more detail in the following chapters.

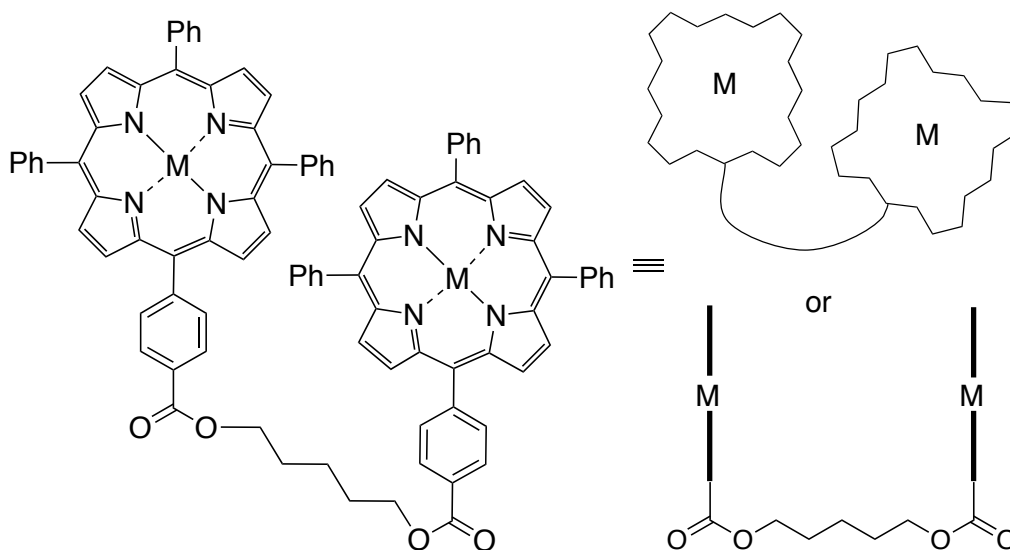


Figure I.27: The porphyrin tweezer as developed by Nakanishi and coworkers and two cartoon representations of the tweezer. M is typically zinc.⁷⁴

I.4: Research Goals for Our ECCD Projects

Through our continuing research with porphyrin tweezers for the determination of absolute configuration, we have gained an insight into the electronic and steric factors that dictate chirality recognition, which has lead to the development of new tweezer systems. Our lab successfully enhanced binding of oxygen functionalities by creating an electron deficient tweezer that was used to determine the configuration of vicinal diols⁷⁵ and epoxy-alcohols.⁷⁶ Also, to elucidate the role of sterics, a series of sterically bulky tweezers were synthesized, suggesting that the phenyl rings of the tweezer are key to chirality recognition.⁷⁷

The goal of our research was multifaceted. From the results of our steric and electronic tuning, a highly fluorinated alkyl substituted porphyrin tweezer was proposed to definitively

prove that the phenyl rings are key for chirality recognition and that the fluorinated substituents are essential to improve substrate binding with the tweezer. A perfluoropropyl substituted tweezer was synthesized, and a collection of diamines, amino alcohols and diols were evaluated. The results of this study confirm the latter hypothesis. To expand the utility of the porphyrin tweezers, new classes of chiral molecules were subjected to ECCD. The results of these analyses have led to the development of mnemonics for chiral heterocyclic alcohols and epoxy-amides. By changing the length of the methylene linker between the metalloporphyrins, the role of tweezer rigidity in chirality transfer was elucidated. We were able to show that ECCD results for flexible guest molecules can be improved by shortening the tweezer linker creating a more rigid host. Finally, there are limited examples of ECCD with substrates bearing a single functionality. A tripodal system was synthesized for the evaluation of primary amines which was shown to form a host-guest complex by NMR.

The end goal of our research is to develop ECCD host systems capable of accepting a wide range of chiral guest molecules and provide consistent and reliable ECCD results with micromolar quantities of chiral substrate. Additionally, we desire a system that is easy to use and lacking the necessity of derivatization so that the scientific community has a convenient and non-empirical method for determining the configuration of an unknown molecule. The results of the studies in this thesis bring us to a better understanding of our current system and provide ideas on how to improve upon the host molecules towards a general and universal host for the determination of absolute stereochemistry for small, chiral organic guest molecules.

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Chapter II

Modulation of Steric and Electronic Parameters of Porphyrin

Tweezers

II.1: Stereochemical Determination with Porphyrin Tweezers

Porphyrins and metalloporphyrins make ideal chromophores for exciton coupled circular dichroism (ECCD) for several reasons.¹⁻³ First, porphyrins are known to have large extinction coefficients ($\epsilon = 440,000 \text{ L mol}^{-1} \text{ cm}^{-1}$ in CH_2Cl_2) as compared to other organic chromophores such as *N,N*-dimethylaminobenzoates ($\epsilon = 28,200 \text{ L mol}^{-1} \text{ cm}^{-1}$ in EtOH). The larger extinction coefficient correlates to more intense ECCD signals generated by the coupling of porphyrins. The absorption maximum (λ_{max}) of tetraphenylporphyrin ($\lambda_{\text{max}} = 417 \text{ nm}$ in CH_2Cl_2) is far separated from the λ_{max} of commonly encountered chromophores of organic molecules such as, olefins ($\lambda_{\text{max}} \approx 180 \text{ nm}$), carbonyls ($\lambda_{\text{max}} \approx 190 \text{ nm}$) and phenyl groups ($\lambda_{\text{max}} \approx 205 \text{ nm}$). Therefore, the porphyrins will not have undesired excitonic coupling with the guest molecule which would cause complex signals in the ECCD spectra.² Finally, a porphyrin is large in size, up to $18 \text{ \AA}$, allowing for coupling over large distances.^{3,4}

The first porphyrin tweezer was developed by Nakanishi and coworkers in 1998.⁵ The Zn-TPP-Tweezer (Zn-TPP-Tz), shown in Figure II.1A, features two zincated 10,15,20-triphenyl-5-benzoate porphyrins linked by 1,5-pentane diol. Upon addition of a chiral diamine to a solution of Zn-TPP-Tweezer, the lone pair of electrons of the amino functionalities coordinate to the zinc centers of the porphyrin by donation into the lowest unoccupied molecular orbital (LUMO) of the zinc. This forms a sandwich type, host-guest complex (Figure II.1B). Once the complex is

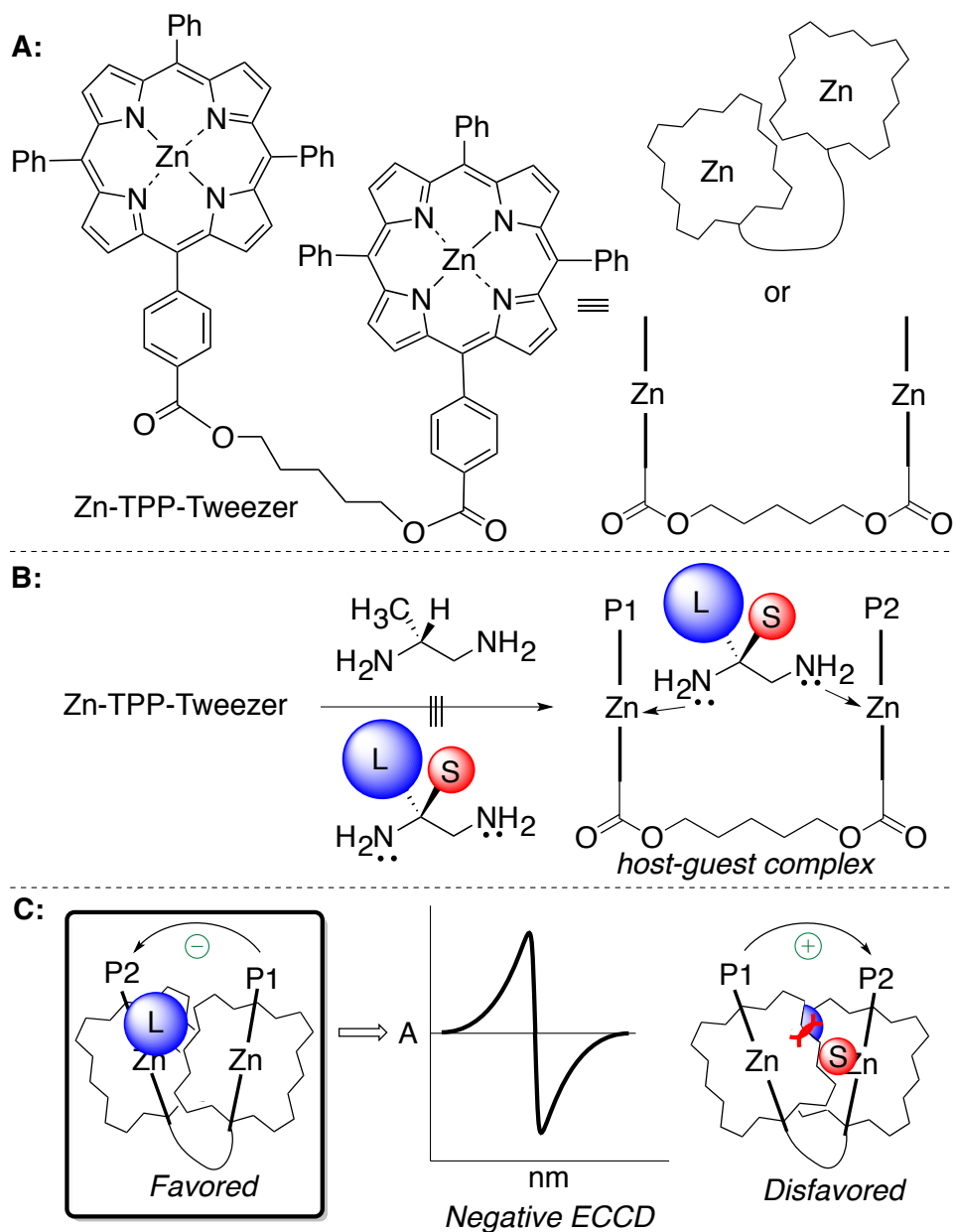


Figure II.1: ECD of chiral diamines using a porphyrin tweezer. **A:** The Zn-TPP-Tweezer and other representations. **B:** Addition of a chiral diamine to Zn-TPP-Tweezer results in a host-guest complex. **C:** The helicity and the sign of the observed ECD signal is a consequence of the point chirality of the diamine. In this case, the porphyrin moves to avoid the large group, blue sphere, generating a counterclockwise helicity and a negative ECD signal.⁵

formed, the point chirality of the guest molecule is translated into the helical chirality of the tweezer. Figure II.1 B depicts the complex formed between Zn-TPP-Tweezer and (*R*)-1,2-diaminopropane. Once the complex has formed, a steric bias is created between the chiral center of the guest molecule and the nearest porphyrin. This bias will determine the relative orientation of the porphyrins. P2, the porphyrin far from the chiral center, will remain static as interaction with the adjacent methylene will not create a steric bias. However, P1, the porphyrin closest to the chiral center will shift. In this case, the porphyrin shifts clockwise toward the smaller hydrogen (red sphere) to avoid interaction with the large methyl group (blue sphere). This creates an overall counterclockwise helicity when looking from P1 to P2, which is expected to generate a negative ECCD signal. With this configuration of the amine, the diastereomeric complex where the porphyrins are in a clockwise arrangement, would result in higher steric interactions as P1 is closer to the large group. This complex is disfavored. As a general rule, the porphyrin interacting with an asymmetric center will shift towards the smallest group at that center. This is the basis for development of ECCD mnemonics for other classes of molecules.

The Zn-TPP-Tweezer was initially used for the determination of configuration for diamines (Figure II.1) and derivatized amino acids and amino alcohols.⁵ In this seminal report using porphyrin tweezers, the mnemonic for diamines was established (see Figure II.1) but a limitation of the tweezer was found. The binding of an oxygen functionality to Zn-TPP-Tz is fairly weak therefore, the carboxylic acid of the amino acid or the alcohol of the amino alcohol was derivatized to an amine containing functionality prior to ECCD analysis. This enhanced the

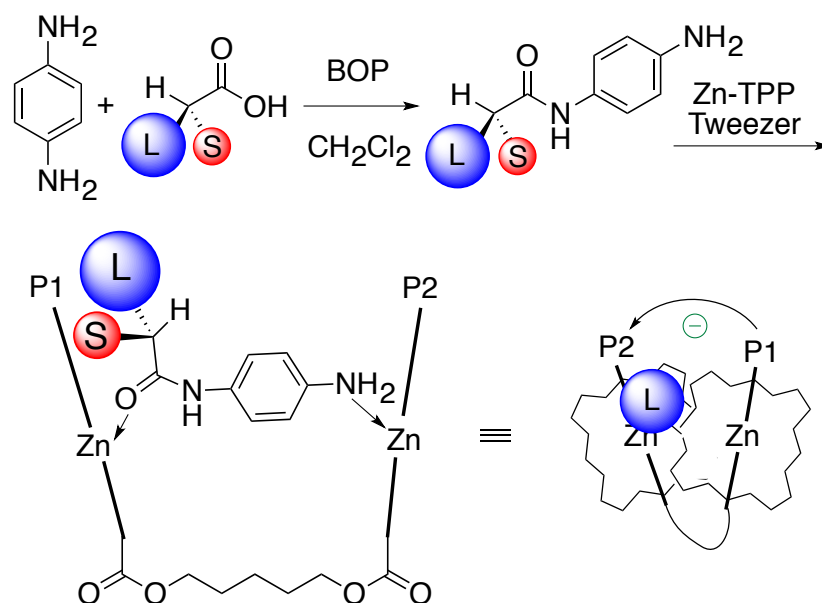


Figure II.2: ECCD system developed the determination of stereochemistry of chiral carboxylic acids. Derivatization installs the nitrogen containing functionalities necessary for binding with Zn-TPP-Tweezer. P1 moves away from the large group generating a counterclockwise helicity of the porphyrins and a negative ECCD signal.¹²

binding of the substrate to the tweezer and improved ECCD signals allowing for development of a general mnemonic for these substrates..

Another limitation of the Zn-TPP-Tweezer is the necessity for the guest molecule to contain two functionalities capable of binding to the zinc centers of the porphyrins. Otherwise, the host-guest sandwich complex, shown in Figure II.1, will not form and the porphyrins will not adopt a helical conformation. Thus, ECCD will not be observed. With this in mind, derivatization was utilized to install the necessary binding sites and develop ECCD protocols with Zn-TPP-Tweezer for chiral amines⁶⁻⁹, alcohols^{7,8} and carboxylic acids¹⁰⁻¹² (Figure II.2). In a report from our laboratory, an ECCD protocol for carboxylic acids was developed by first employing a BOP mediated coupling with *p*-phenylenediamine to bring in the necessary amine

binding functionalities. When the derivatized carboxylic acid was added to Zn-TPP-Tweezer, lone pair of electrons of the oxygen of the amide carbonyl and the free amine bound to the zinc centers of the porphyrins. The ECCD signal observed was a result of the porphyrin moving away from the large group at the chiral center. Accordingly the example in Figure II.2 is expected to generate a negative ECCD and the opposite configuration would provide a positive ECCD.

In 2000, Inoue and coworkers reported a porphyrin based host molecule capable of sensing the chirality of monoamines without derivatization.^{13,14} This porphyrin dimer, composed of two zincated octaethylporphyrins brought together by a two methylene linker, was found to have a different mechanism of sensing chirality than that of the Zn-TPP-Tweezer. The resting state of the dimer is an open conformation where the porphyrins are held in close proximity by the short linker. The amine binds to the zinc center of one porphyrin, P2, such that the largest group of the chiral center is *anti* to the porphyrin P1, forcing the other two groups of the chiral center toward P1 (Figure II.3). The chirality of the amine is sensed by the

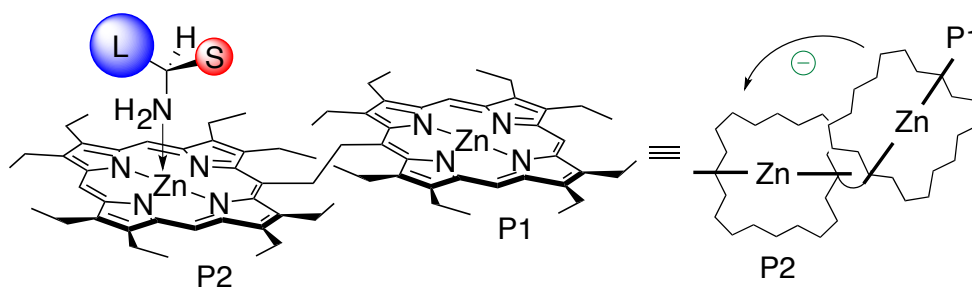


Figure II.3: Inoue's porphyrin dimer for the determination of chirality for monoamines via ECCD. Steric interactions between the amine and the ethyl groups of P1 force P1 to rotate toward the hydrogen creating a counterclockwise helicity of the porphyrins and a negative ECCD signal.

protruding ethyl substituents of P1. To adopt a favorable conformation, P1 rotates toward the hydrogen causing a counterclockwise helicity of the porphyrins. An amine of this configuration would produce a negative ECCD signal and the opposite configuration would give positive ECCD. In 2002, the authors extended the methodology to include monoalcohols by changing the zinc centers to magnesium.¹⁵ Magnesium has a high affinity for oxygen allowing for tighter binding of the alcohol and in turn, observable ECCD signals.

II.2: Modulation of Steric and Electronic Parameters of the Porphyrin Tweezer Toward a More Robust Host System

The three dimensional structure of tetraphenylporphyrin has been known since 1963 when Fleischer solved the crystal structure of copper tetraphenylporphyrin.¹⁶ This structure showed that the porphyrin ring is essentially planar and the *meso* phenyl substituents lie perpendicular to the porphyrin ring. For the Zn-TPP benzoate¹⁷ and presumably the Zn-TPP-Tweezer, this is also true (Figure II.4, methyl ester is shown). The phenyl rings lie perpendicular to the porphyrin rings and protrude into the binding pocket where the chiral substrate binds to the zinc centers. It is thought that the interaction between the *meso* phenyl rings and the chiral center of the substrate creates the steric bias that drives the transfer of chirality from the substrate to the tweezer. To gain a better understanding of the role of the sterics in chirality recognition when the host-guest complex forms, Dr. Marina Tanasova synthesized a series of tweezers based on the Zn-TPP-Tweezer scaffold.¹⁸ With the hypothesis that increased steric bulk of the phenyl rings would enhance the transfer of chirality from the guest to the host, the *meso* phenyls of Zn-TPP-Tweezer were replaced with sterically larger phenyl groups such as

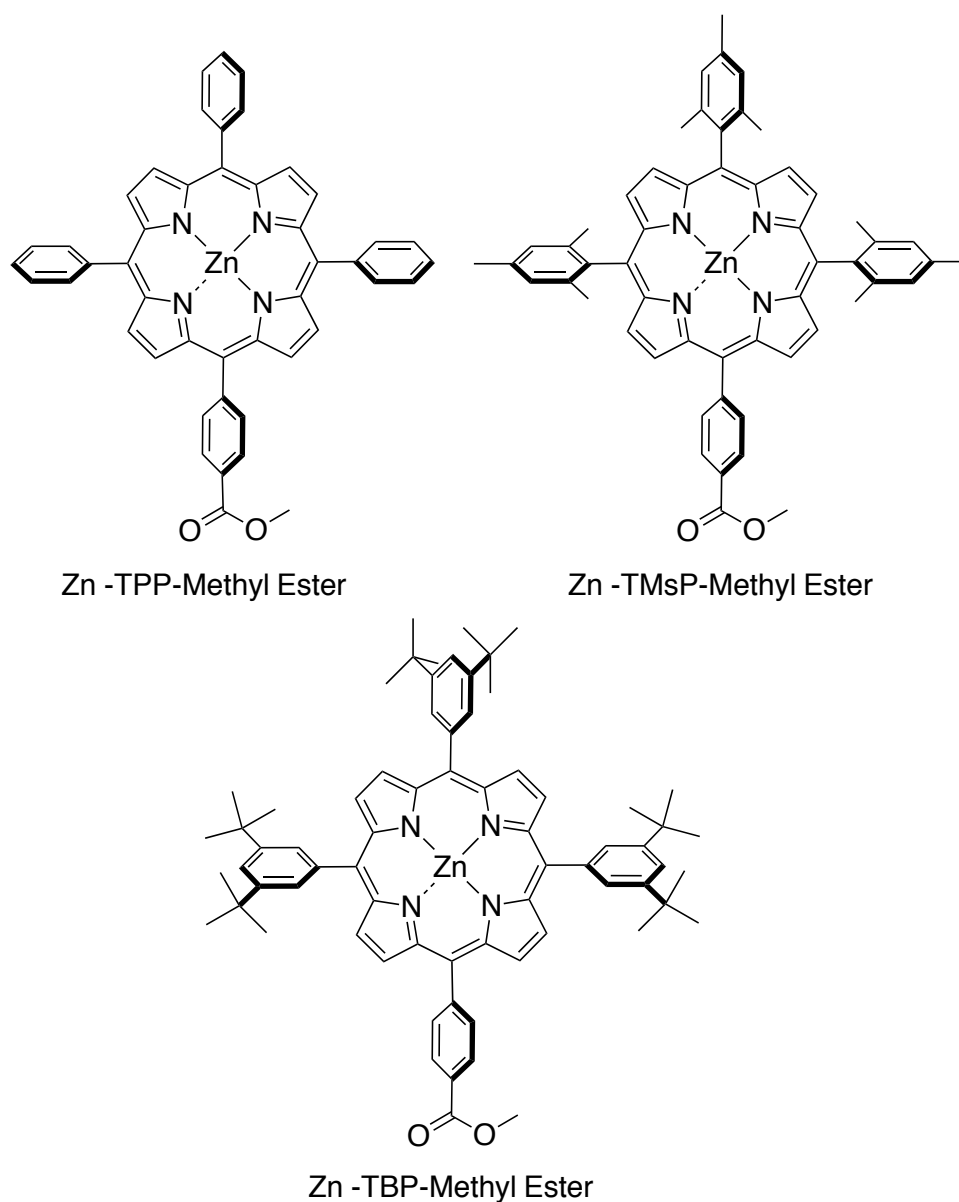


Figure II.4: The original tweezer scaffold as represented by Zn-TPP-Me Ester and selected examples from the study of tweezer steric interactions. The steric influence of the phenyl substituents is enhanced by the methyl groups of Zn-TMsP-Me Ester and *tert*-butyl groups of Zn-TBP-Me Ester.¹⁸

mesityl, Zn-TMsP-Tweezer, and the 3,5-di-*tert*-butylphenyl, Zn-TBP-Methyl Ester (Figure II.4 shows the corresponding zincated methyl esters).

Zn-TMsP-Methyl Ester was designed to enhance the interaction with the chiral center of the guest molecule by introduction of methyl groups at the *ortho* position of the *meso* phenyls. In theory, the methyls, which are larger than the hydrogens of Zn-TPP-Tweezer, should cause larger steric interactions with the chiral center of the substrate, which should force the porphyrin further away from the large group. In doing so, the angle between the chromophores and the ECCD amplitude should increase. However, the results showed smaller ECCD amplitudes for most substrates as compared to Zn-TPP-Tweezer (Figure II.5A). Additionally, smaller binding constants for the substrates with Zn-TMsP-Tweezer were observed. The weaker binding and less reliable ECCD signals are thought to be a result of the methyl groups blocking access to the zinc center thereby preventing formation of the host-guest complex (Figure II.5 B).

The most successful tweezer from this study, in terms of ECCD amplitudes, was the Zn-TBP-Tweezer designed with 3,5-di-*tert*-butyphenyl substituents at the *meta* positions of the *meso* phenyl groups. For most of the substrates evaluated, the ECCD amplitudes with Zn-TBP-Tweezer were larger than those observed for Zn-TPP-Tweezer (Figure II.5 A). Energy minimization of the complex of Zn-TBP-Tweezer with (*S*)-1,2-diaminopropane indicated that there was not an increase in porphyrin-substrate interaction as the *tert*-butyl groups are oriented away from the binding pocket. However, a significant porphyrin-porphyrin interaction was found. The *tert*-butyl groups are believed to interact, forcing the porphyrins further away from one another. This driving force increases the angle between the chromophores (ψ , Figure II.5 C) and as a consequence, the ECCD amplitudes increased without affecting the binding of the guest. The results of this study showed that steric interactions of the *meso* phenyl

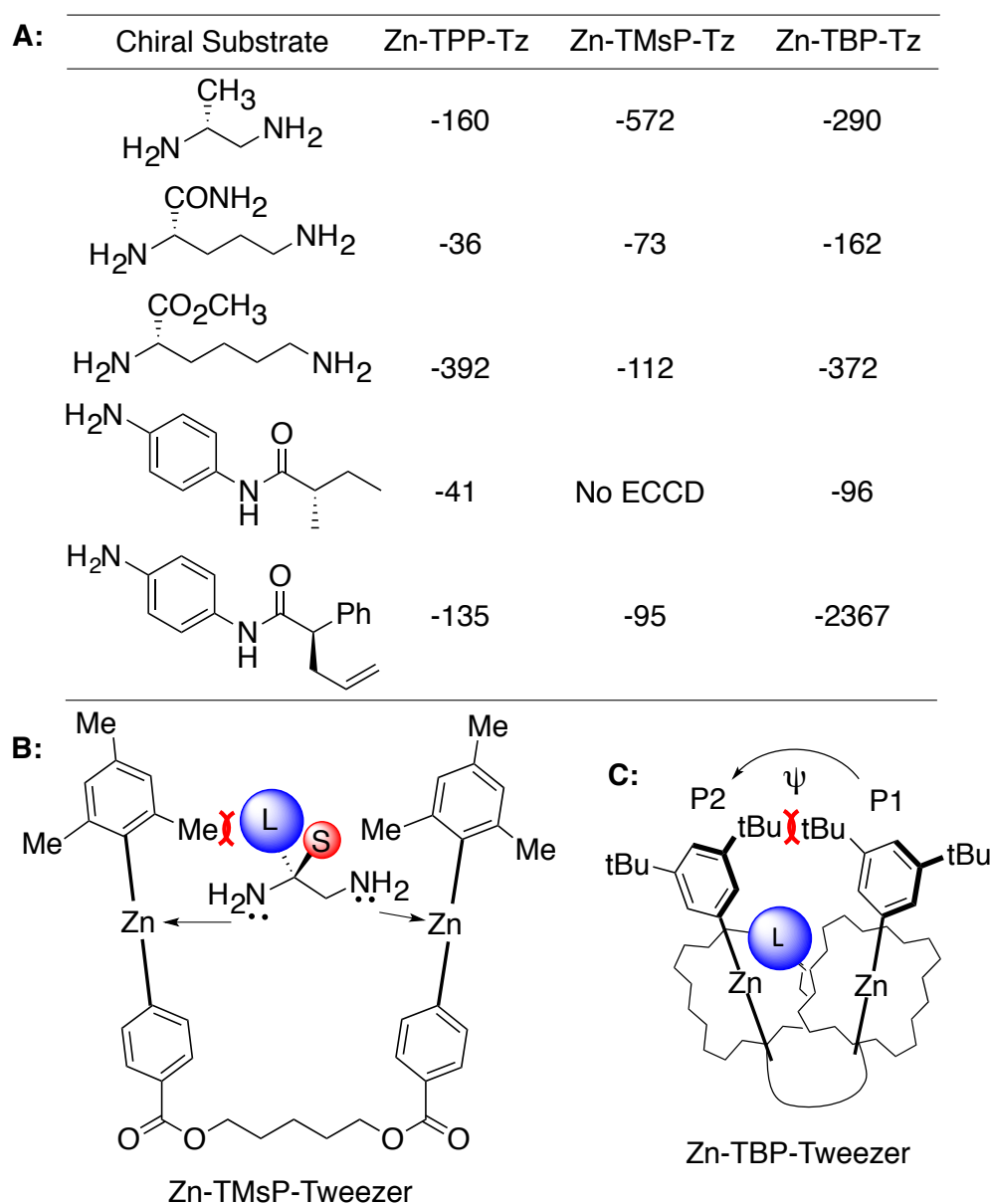


Figure II.5: Selected ECCD results of the steric study. **A:** Selected ECCD values. In general Zn-TMsP-Tweezer provided the smallest signals and Zn-TBP-Tweezer gave the largest amplitudes. **B:** Binding of a substrate to Zn-TMsP-Tweezer is hindered by the methyl groups. **C:** The *tert*-butyl groups cause porphyrin-porphyrin interaction that forces the a larger value of ψ , the angle between the porphyrins.¹⁸

substituents will effect ECCD amplitudes, which will be useful for the design of more steric-sensitive tweezers.

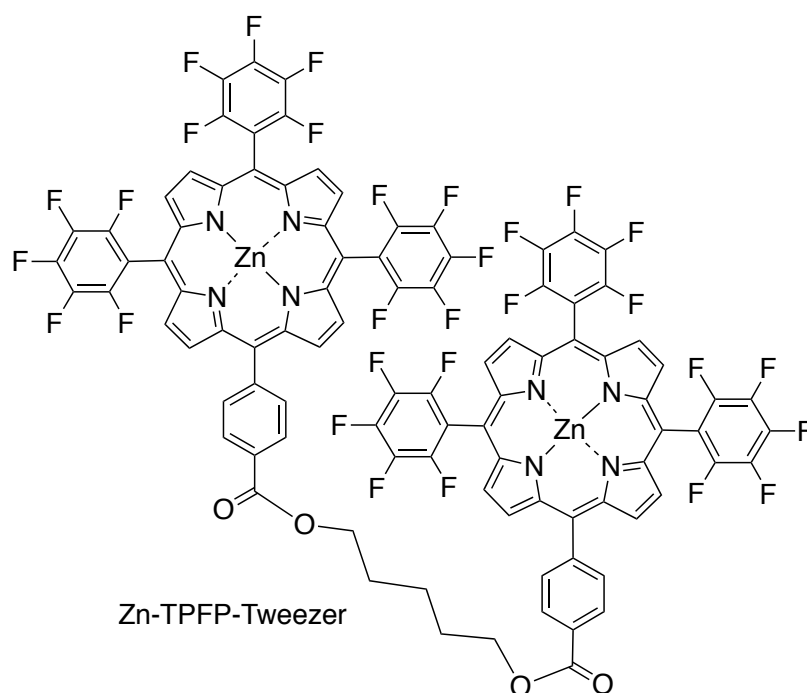
Another platform for optimization of the Zn-TPP-Tweezer is by tuning the electronics of the porphyrins. An electron deficient porphyrin would withdraw electron density from the zinc center, enhancing the Lewis acidity of the metal.¹⁹ This could allow for stronger interactions between the zinc and the substrate. Being that weak binding of oxygenated functionalities to Zn-TPP-Tweezer was a known limitation, a more robust tweezer was desired to expand the substrate scope of ECCD analysis to include oxygenated functionalities. It was hypothesized that an electron deficient tweezer could resolve this issue. As a part of his thesis work, Dr. Xiaoyong Li synthesized a series of tweezers where the *meso* phenyl substituents were replaced by substituted phenyl groups of varying electron donating or withdrawing capabilities.^{19,20} As the electron withdrawing ability of the *meso* phenyl was increased, tighter binding to the substrate and more consistent ECCD signals were observed. The highly fluorinated tweezer, Zn-TPFP-Tweezer (Figure II.2) was the most consistent of the tweezers synthesized and was used for the determination of absolute configuration vicinal diols. Furthermore, this was the first ECCD system shown effective for *erythro* diols, which had not succumbed to other means of interrogation.

To support the idea that increasing the electron deficiency of the porphyrin would increase the Lewis acidity of the zinc center, the LUMO energy for the zinc center of Zn-TPP-Methyl Ester and Zn-TPFP-Methyl Ester were calculated.¹⁹ It was found that the LUMO of Zn-TPFP-Methyl Ester was a lower in energy than that of Zn-TPP-Methyl Ester. This correlates to a stronger interaction between the zinc of Zn-TPFP-Methyl Ester and the substrate because the

LUMO of Zn-TPFP-Methyl Ester is closer in energy to the lone pair of electrons of the binding functionality of the substrate. In other words, the Zn-TPFP-Methyl Ester is a stronger Lewis acid. The increased Lewis acidity promotes tighter binding of the substrate to the tweezer creating a more rigid host-guest complex. A flexible host-guest complex, one with weak substrate binding, is thought to access a number of ECCD active conformations as the weak binding allows for more degrees of freedom for the complex. Therefore, the porphyrins are not fixed in a single conformation and it is possible to access complexes with opposite helical chirality. The summation of all the accessible complexes results in weak or no ECCD signal. The enhanced binding observed for Zn-TPFP-Methyl Ester would translate into enhanced substrate-tweezer binding, a rigidified complex and fewer degrees of freedom for the complex. This means that there are fewer available ECCD active complexes and in turn, the rigidified complex provides more intense and reliable ECCD signals. Figure II.2 gives selected ECCD data for vicinal diols. In all cases, Zn-TPFP-Tweezer provided stronger ECCD amplitudes than Zn-TPP-Tweezer. Dr. Li also employed Zn-TPFP-Tweezer for the stereochemical determination of epoxy alcohols.²¹

II.3: Design and Synthesis Toward an Unsubstituted Porphyrin Tweezer

The results of the study on steric factors showed that an increase in steric interaction between the porphyrin rings increases the ECCD amplitudes.¹⁸ However, it does not definitively prove that the *meso* phenyl substituents are required for chirality recognition. Therefore, a tweezer with hydrogen substituents at the *meso* positions was proposed. It was hypothesized that without the phenyl rings, weak ECCD signals will be observed. If the *meso*

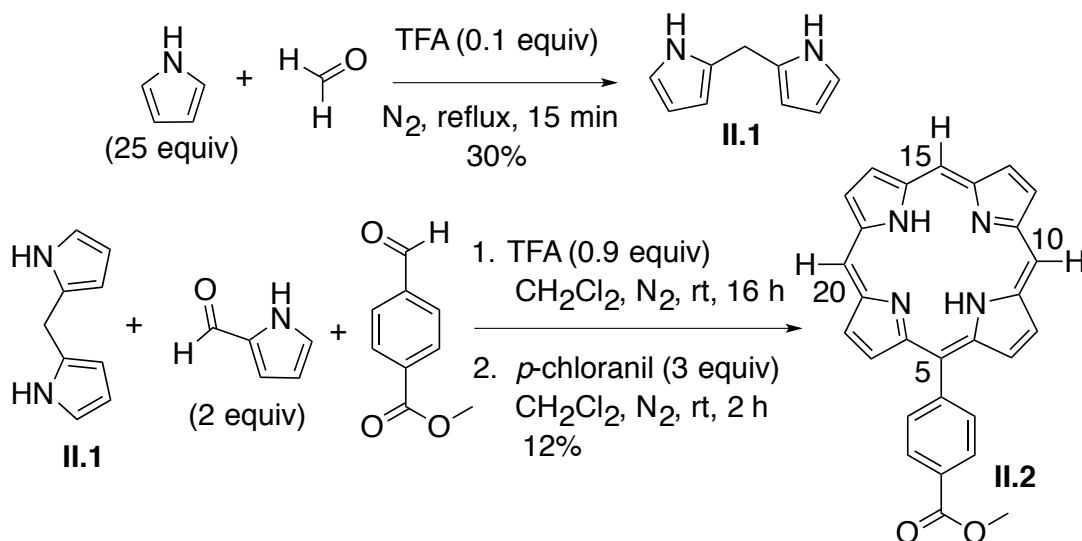


Chiral Substrate	Zn-TPP-tz	Zn-TPFP-tz
	-16	-79
	No ECCD	+33
	No ECCD	-41
	No ECCD	-50

Figure II.6: The Zn-TPFP-Tweezer and selected ECCD results. For the substrates evaluated, ECCD results were observed with Zn-TPFP-Tweezer when Zn-TPP-Tweezer failed. These results are explained by tighter binding of the substrate due to the increased Lewis acidity of the zinc which is a consequence of the electron deficient porphyrin.¹⁹

phenyls are interacting with the chiral center of the substrate and thereby are the driving force for transfer of chirality to the tweezer then by changing the *meso* phenyls to hydrogens, the interaction between the substrate and the tweezer should be eliminated. There is the possibility that small signals may be observed due to the phenyl at the 5 position where the linker is attached to the porphyrins (Scheme 1). Nevertheless, the observed signal should be significantly smaller than the signals observed with tweezer Zn-TPP-Tweezer.

Synthesis of this tweezer was attempted following the literature preceded procedure for monosubstituted porphyrins.²² The methyl ester of the porphyrin monomer would be obtained from an acid catalyzed condensation of pyrrole, 4-formylmethylbenzoate and the appropriate aldehyde. The methyl ester is then subjected to hydrolysis under basic conditions providing the porphyrin acid.¹⁸ The monolinker is obtained from an EDC coupling of the porphyrin acid and 1,5-pentane diol. Subsequent EDC coupling of the monolinker and



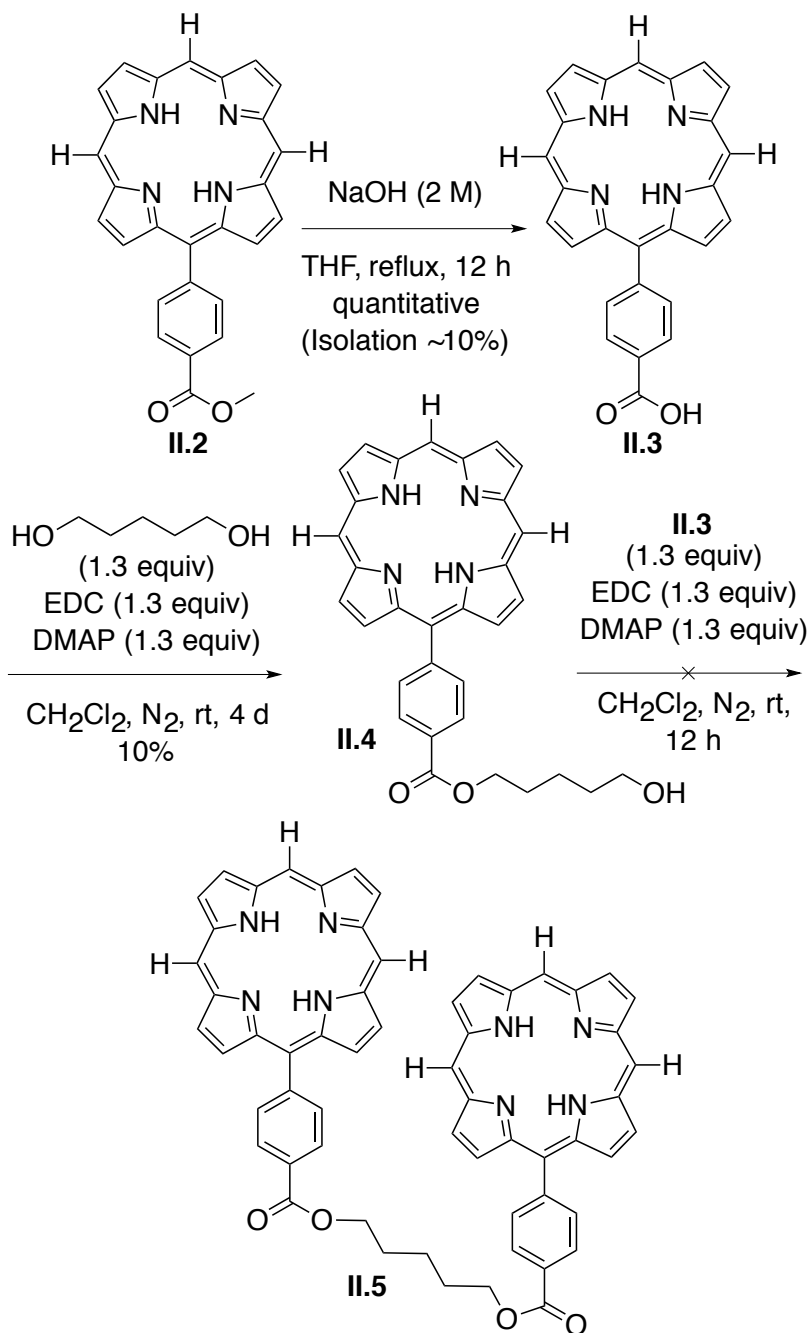
Scheme II.1: Synthesis of the unsubstituted dipyrromethane and porphyrin methyl ester.

porphyrin acid provides the free tweezer.⁵ Finally, zincation of the tweezer with zinc II acetate would provide the zincated tweezer.¹⁸

For the unsubstituted porphyrin tweezer, a two step process to the porphyrin methyl ester was derived from a procedure reported by Lindsey and co-workers (Scheme II.1).²² First, an acid catalyzed condensation of pyrrole and paraformaldehyde provided the unsubstituted dipyrromethane (**II.1**). Then a condensation of the dipyrromethane, pyrrole-2-carboxaldehyde and terephthalaldehydic methyl ester and subsequent oxidation would yield the unsubstituted porphyrin methyl ester (**II.2**) in 12% yield overall.

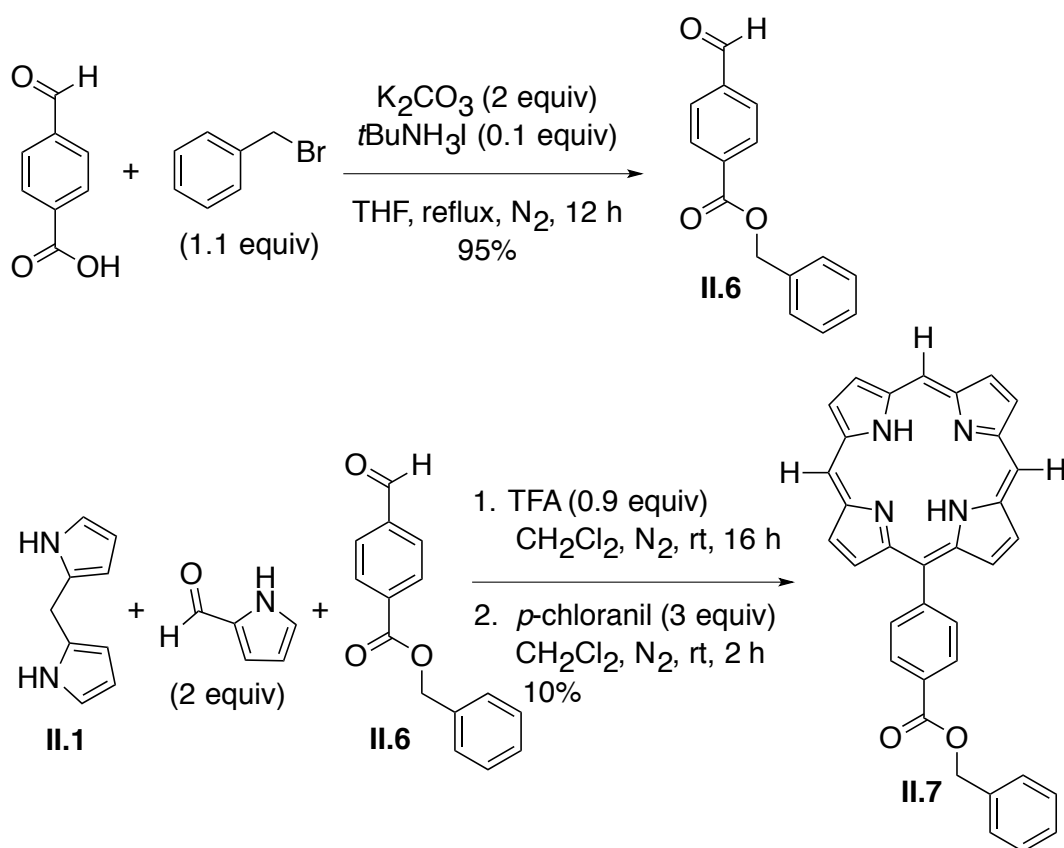
Unfortunately, the hydrolysis of **II.2** proved problematic. The porphyrin acid (**II.3**) was completely soluble in water and sparingly soluble in organic solvents. Extraction of **II.3** was attempted with diethyl ether, tetrahydrofuran, dichloromethane, chloroform and ethyl acetate. However, only limited quantities of **II.3** could be extracted in ethyl acetate with considerable loss of **II.3** in the process. The initial EDC coupling of **II.3** and 1,5-pentane diol to the monolinker (**II.4**) did yield the desired product albeit in low yields (10%). Typically dichloromethane is the solvent of choice for the coupling reaction, however the limited solubility of **II.3** caused low yields. The monolinker obtained was subjected to the second coupling in an effort to obtain the free tweezer (**II.5**). Unfortunately, after several failed attempts with EDC and DCC the free tweezer was not isolated (Scheme II.2). This was not entirely unexpected. With other tweezer systems, the yield of the free tweezer coupling is lower than the yield of the monolinker coupling. Being that the yields to obtain **II.4** were low, it was anticipated that the second coupling would be even lower. In this case, the second

coupling fails to provide the desired product. Following the failure of the traditional tweezer synthesis. Alternative pathways to the tweezer were envisioned.



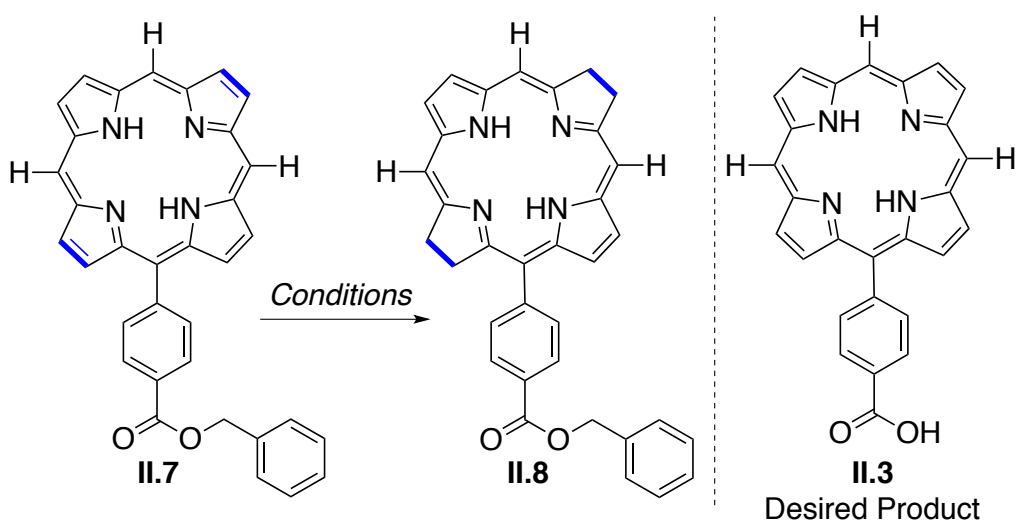
Scheme II.2: Attempted synthesis of the unsubstituted porphyrin tweezer with the problematic basic hydrolysis of the methyl ester.

First, knowing the solubility of the acid in water was problematic, an alternate pathway to avoid aqueous reaction conditions was desired. As a potential solution, the unsubstituted porphyrin benzyl ester was designed. Unlike the methyl ester, the benzyl ester could be deprotected under hydrogenolysis conditions to yield the acid. Once the reaction is complete, filtration could allow for separation of the acid from the metal catalyst. In this way, the acid would be obtained without being exposed to an aqueous environment. Synthesis of the unsubstituted porphyrin benzyl ester began with the synthesis of 4-formyl benzylbenzoate (**II.6**, Scheme II.3) from 4-formyl benzoic acid and benzylbromide. The condensation of dipyrromethane, pyrrole-2-carboxaldehyde and the benzylbenzoate and subsequent oxidation provided the desired porphyrin benzyl ester (**II.7**) in 10% yield.



Scheme II.3: Synthesis of the unsubstituted porphyrin benzyl ester.

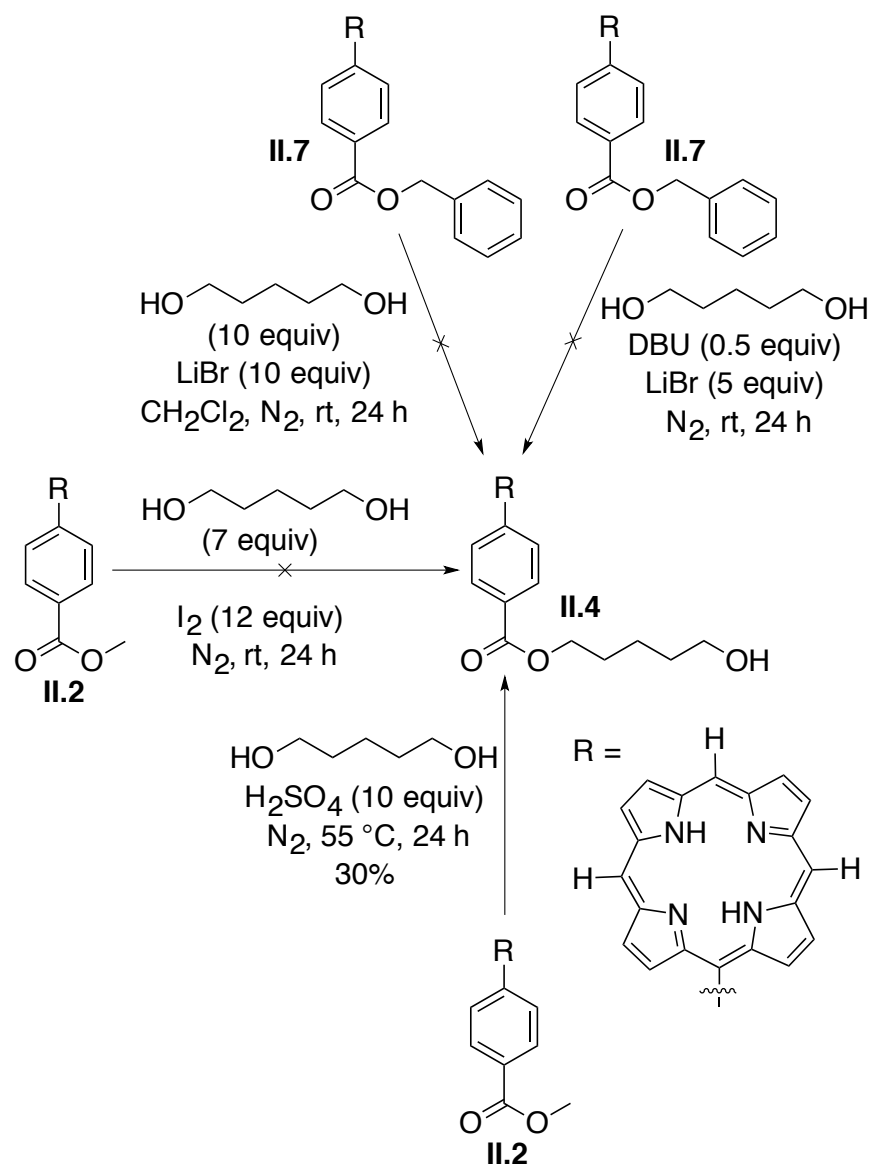
With **II.7** in hand, the hydrogenolysis was attempted under a variety of reaction conditions (Table II.1). Commonly, hydrogenolysis is conducted with palladium on charcoal (Pd/C) and hydrogen. Therefore, these were the first conditions used. Unfortunately, in dichloromethane a decomposition product was isolated as the major product. Next, the solvent was changed. Again, in ethyl acetate and ethanol, a single decomposition product was



Entry	Catalyst	Solvent	H ₂ Source	Result
1	Pd/C	CH ₂ Cl ₂	H ₂	II.8
2	Pd/C	EtOAc	H ₂	II.8
3	Pd/C	EtOH	H ₂	II.8
4	Pd/C	EtOH	1,4-cyclohexadiene	No Reaction
5	Pd(OH) ₂	CH ₂ Cl ₂	H ₂	II.8
6	Pd(OH) ₂	EtOAc	H ₂	II.8
7	Pd(OH) ₂	EtOH	H ₂	II.8
8	Pd(OH) ₂	EtOH	1,4-cyclohexadiene	No Reaction

Table II.1: Hydrogenolysis of the unsubstituted porphyrin benzyl ester. All reactions rt, 0.004 M (substrate), H₂ balloon, 10 mol% catalyst, 1 hour.

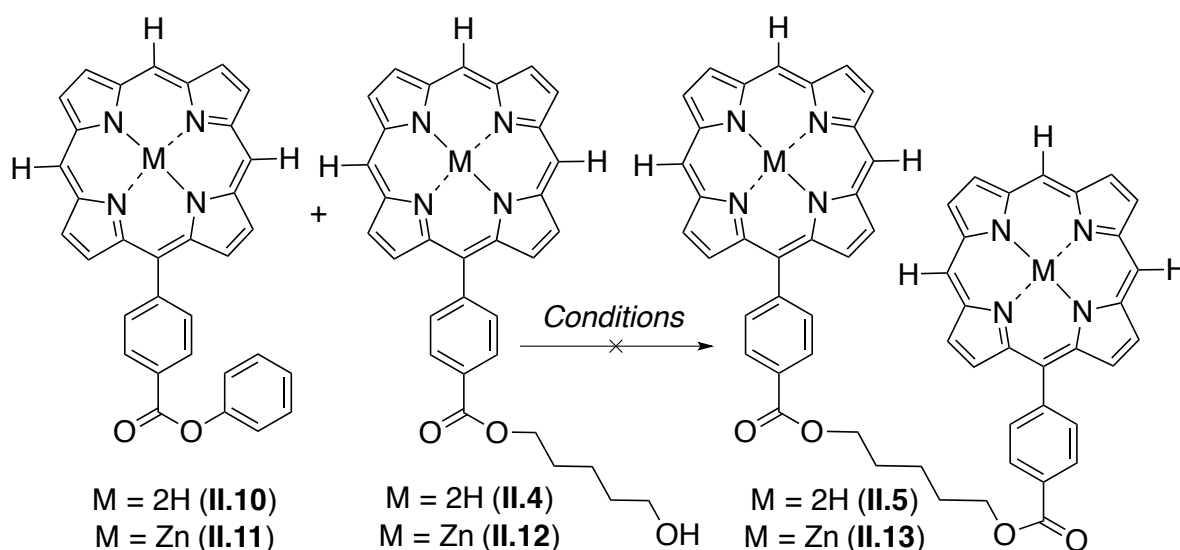
isolated. Interestingly, the NMRs of the isolated species was the same for all three reactions. By NMR, it was determined that this product retained the benzyl ester however, several aromatic peaks of the porphyrin moved upfield. To prevent the over-reduction of the porphyrin, both the catalyst and the hydrogen source were changed. First, a less active



Scheme II.4: Attempted transesterification reactions to generate the unsubstituted porphyrin monolinker from the benzyl and methyl esters.

palladium catalyst, Pearlman's catalyst ($\text{Pd}(\text{OH})_2/\text{C}$), was employed. Once again over-reduced product was isolated. In a final attempt, a less active hydrogen source was used. However, no reaction was observed with 1,4-cyclohexadiene. Further analysis of the undesired product indicated that the two double bonds in the porphyrin that are cross-conjugated with the aromatic system are hydrogenated under these conditions. These cross conjugated double bonds of the porphyrin have been the target of hydrogenation²³⁻²⁷, oxidation²⁸⁻³³, Diels-Alder³⁴⁻³⁷ and 1,3-dipolar cycloaddition³⁸⁻⁴⁷ reactions to yield chlorins and bacteriochlorins. Therefore, the undesired reduction is likely unavoidable and this route was abandoned.

Following the debenzylolation attempts, transesterification of the unsubstituted porphyrin ester was explored as a means of directly synthesizing the monolinker thereby circumventing the unsubstituted porphyrin acid. At first the methyl and benzyl esters were submitted to transesterification conditions. Both Lewis base mediated and base catalyzed (Scheme II.4) conditions were used with no success.^{48,49} Acid catalyzed conditions were moderately successful but only if the alcohol was the solvent.⁵⁰ The limited success of these methods were attributed to the leaving group of the ester. In both cases, an alkyl alcohol (1,5-pentanediol) must displace an alkyl alcohol (benzyl alcohol or methanol). The leaving group ability for all three alcohols should be approximately the same therefore, there is no driving force for the reaction to proceed unless the 1,5-pentane diol is present in large excess (as the solvent). To improve the leaving group ability of the ester alcohol, the unsubstituted phenyl ester was synthesized. For the phenyl ester, phenol is the alcohol being displaced by the 1,5-pentane diol. Phenol is a better leaving group than the diol therefore, the transesterification should proceed to generate the desired monolinker product. Synthesis of the phenyl ester



Entry	M	Base	Solvent
1	2 H	NaH	THF
2	2 H	KHMDS/HMPA	THF
3	2 H	KHMDS/HMPA ^a	THF
4	Zn	NaH	THF
5	Zn	NaH	CH ₂ Cl ₂
6	Zn	KHMDS/HMPA	THF

Table II.2: Unsuccessful transesterification reactions to yield the porphyrin tweezer. All reactions at rt, under N₂, large excess of base, 8h. a: 20 equiv dibenzo-18-crown-6 ether.

The transesterification of the phenyl ester with 1,5-pentandiol under basic conditions, sodium hydride (NaH), proceeded in high yield (Table II.2). Encouraged by this result, a second transesterification of the monolinker with the porphyrin phenyl ester was attempted to give the tweezer. In all cases, the desired tweezer was not generated; instead, the starting materials were isolated. Fearing that the base was being consumed by deprotonating the porphyrin, the transesterification was attempted with the zincated monolinker and the zincated phenyl ester.

Again these reactions were unsuccessful. The failure of the transesterification to yield the tweezer could be due to two factors: 1. the reaction concentration and 2. local concentration of the nucleophile. The transesterification yielding the monolinker is conducted with a large excess of the diol therefore, increasing the probability of the deprotonated diol and the phenyl ester meeting in solution. For the second transesterification, a 1:1 ratio of monolinker nucleophile and phenyl ester must be used due to the limited quantities of the porphyrins available thus reducing the probability of the two meeting. As an additional complication, when the monolinker is deprotonated, the alkoxide formed is six atoms from an ester functionality. The intramolecular attack of the alkoxide on the ester could occur due to an increased local concentration of the nucleophile. This reaction could slow or prevent the transesterification from occurring by using the alkoxide in unproductive pathways.

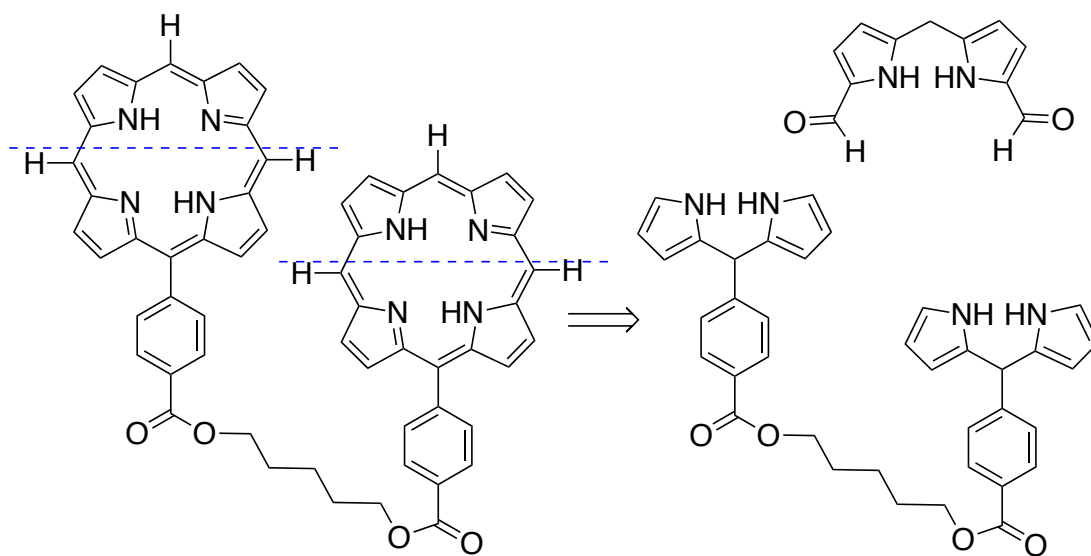
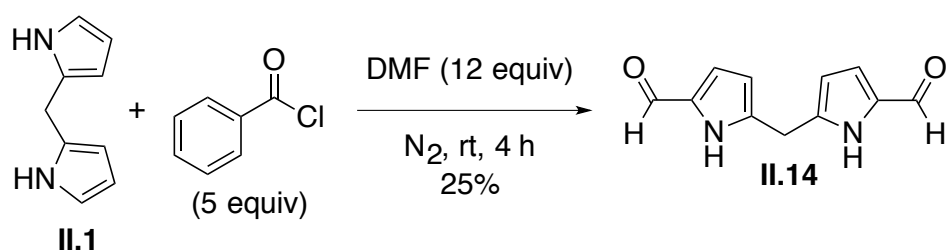


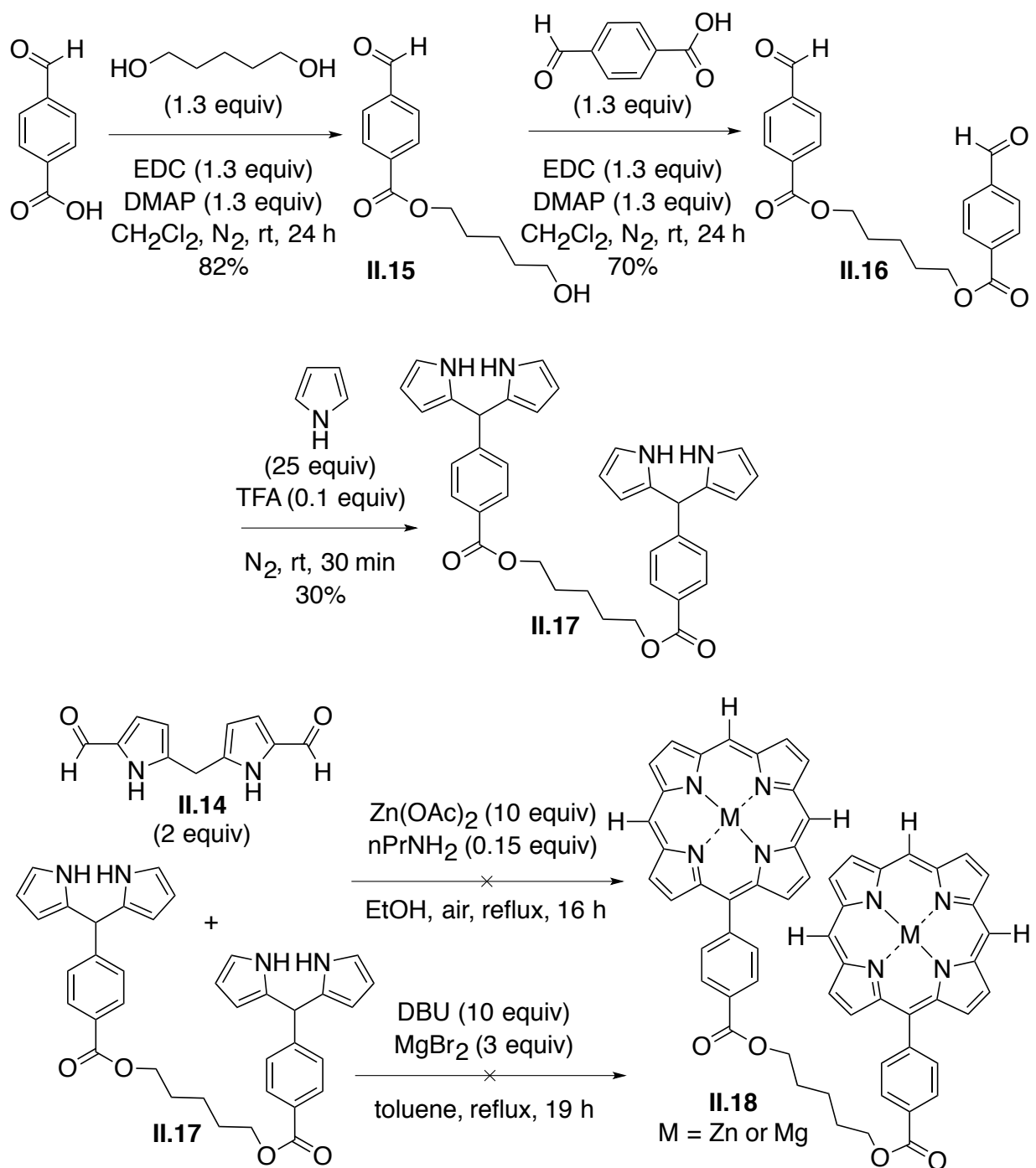
Figure II.7: Retrosynthesis of the unsubstituted porphyrin tweezer splitting the tweezer into top and bottom halves.

A final attempt to the unsubstituted porphyrin tweezer involved splitting the tweezer in half through the porphyrins (Figure II.7). The top and bottom halves would be synthesized separately with the porphyrin condensation left to the last step. The benefit to this route is that the coupling reactions to install the methylene linker would be completed with the commercially available 4-formylbenzoic acid which is more soluble in organic solvents than the porphyrin acid. To build the top half, the dipyrromethane, **II.1**, was subjected to a modified Vilsmeier-Haack formylation to form the 5,5'-diformyl-2,2'-dipyrromethane, **II.14**, in rather low yields.^{51,52}

Synthesis of the bottom half began with the sequential EDC couplings of 4-formylbenzoic acid to 1,5-pentane diol to yield pentane-1,5-diyl bis(4-formylbenzoate), **II.16**. Next, condensation with pyrrole gave the bis-dipyrromethane, **II.17**, to form the base of the tweezer. The condensation of **II.14** and **II.17**, if successful, would have generated the metallated tweezer. The typical yield for the synthesis of a single porphyrin is typically 10-20%. However, in this case the synthesis would create two porphyrins and so the yield would drop to 1-4%. The product, if formed could not be isolated. This tweezer was abandoned due to the synthetic issues.



Scheme II.6: Synthesis of 5,5'-bis formyl-2,2'-dipyrromethane.



Scheme II.7: Attempted synthesis of the unsubstituted tweezer.

II.4: Design and Synthesis of the Perfluoroalkyl Porphyrin Tweezer

From the results of the steric and electronic tuning of the porphyrin, a series of “super-tweezers” were proposed. Of these suggested tweezers, the *meso* perfluoroalkyl porphyrin tweezer, Zn-C₃F₇-Tweezer (Zn-C₃F₇-Tz), was intended to serve a dual purpose (Figure II.8, Me Ester is shown). First, this tweezer was designed to test our hypothesis that substrate binding affinities can be correlated to the E_{LUMO} energies of the zinc center of the porphyrin. Specifically that binding affinities are higher for tweezers with lower E_{LUMO} energy. Being that the LUMO energy of the Zn-C₃F₇-Tweezer is larger than both Zn-TPP-Tweezer and Zn-TPFP-Tweezer, smaller binding affinities are anticipated. Second, this tweezer differs from all others in that three of the *meso* substituents are alkyl chains. Alkyl chains have more degrees of freedom than do phenyl rings and it was expected that with a substrate bound, this chain would rotate out of the binding pocket of the tweezer to minimize interactions with the substrate. By minimizing host-guest interactions, the transfer of point chirality of the substrate

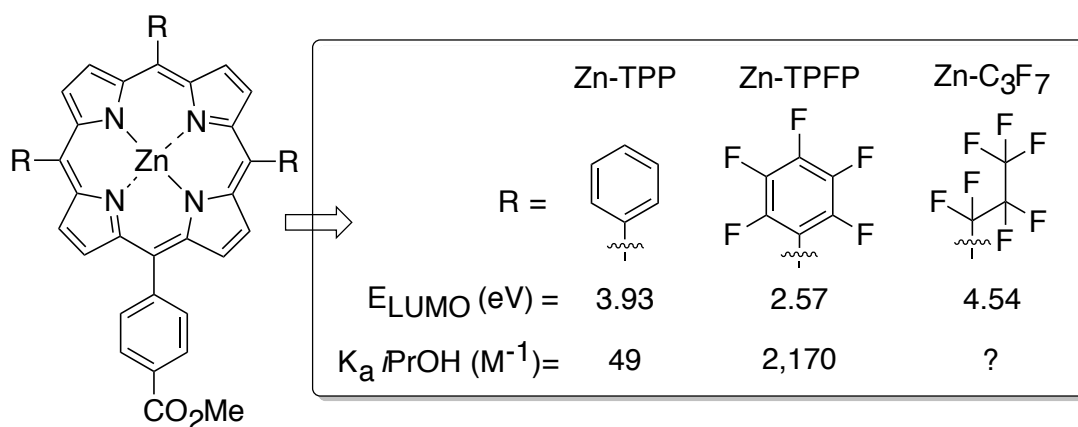
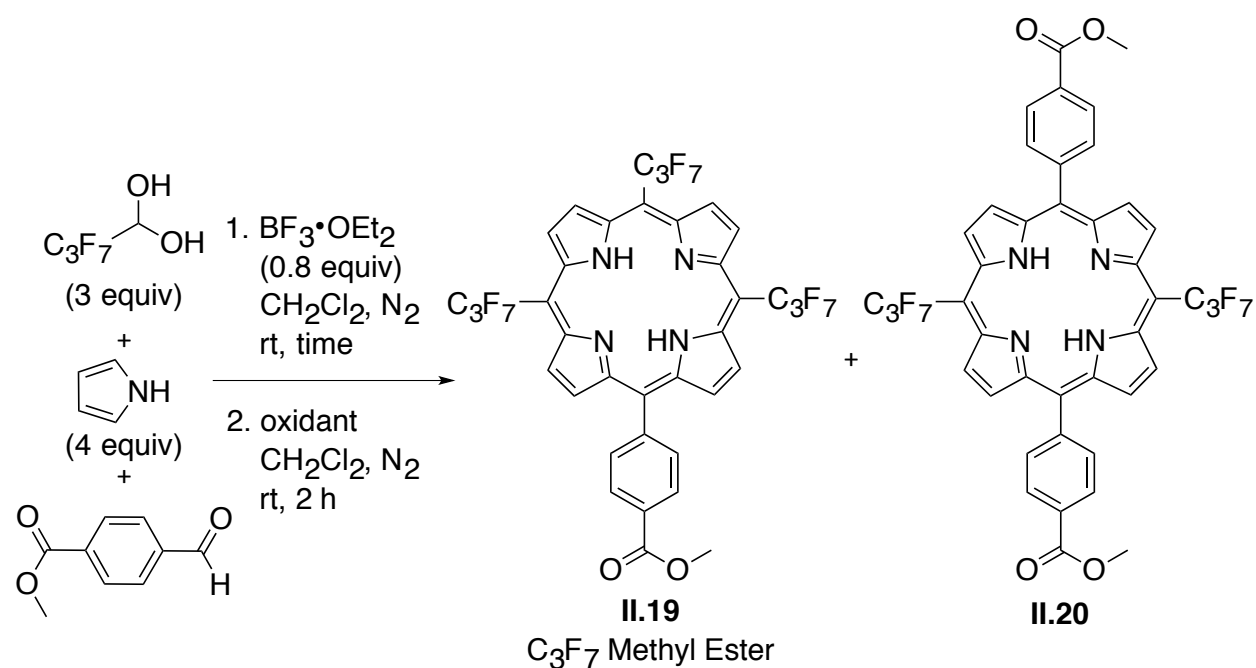


Figure II.8: Structures of the Zn-TPP, Zn-TPFP and Zn-C₃F₇ Me Esters. E_{LUMO} and binding constants (with isopropyl alcohol) indicate as the energy of the LUMO drops, binding affinity increases.

to helical chirality of the tweezer should be inefficient at best. Thus, any ECCD signals observed should be of smaller amplitude with this tweezer as compared to Zn-TPP-Tweezer or Zn-TPFP-Tweezer. The comparison of ECCD results with these three tweezers should elucidate the role of the phenyl rings in chirality transfer.

For this study, the 10,15,20-tris(2,2,3,3,4,4,4-heptafluoropropyl)-5-(4-benzoate) porphyrin was designed to take advantage of the commercially available aldehyde. The synthesis of the perfluoroalkyl tweezer was designed to follow the procedure developed for the synthesis of TPFP tweezer.¹⁹ Zincation of the free C₃F₇-tweezer would provide Zn-C₃F₇-Tweezer, the host system for ECCD analysis. The free tweezer is the product of sequential ECCD couplings of the C₃F₇ porphyrin acid and 1,5-pentane diol. The acid would be obtained from hydrolysis of the C₃F₇ methyl ester.

Attempts to synthesize the heptafluoropropylporphyrin methyl ester (**II.19**) by condensation of 4-formylmethyl benzoate, pyrrole and perfluorobutyraldehyde hydrate following the procedure for synthesis of TPFP methyl ester were largely unsuccessful. However, under modified reactions conditions, this method provided the *trans* dimethyl ester porphyrin (**II.20**) as the major product (Table II.3). This was unfortunate considering that **II.19** is required for construction of the tweezer. It was reasoned that the aldehyde of 4-formyl methyl benzoate is likely more reactive than hydrated aldehyde of the perfluorobutyraldehyde. Therefore, the pyrrole is likely reacting preferentially with the benzoate and preventing formation of the desired porphyrin. To remedy this problem, the perfluorobutyric hydrate and the pyrrole were allowed to react in the presence of boron trifluoride diethyl etherate (BF₃•OEt₂) for 4 hours prior to the addition of the methyl 4-formylbenzoate. Under these

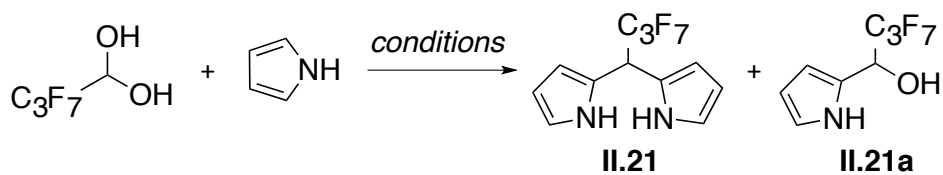


Entry	Time (h)	Oxidant	Yield % (19/20)
1	2	<i>p</i> -chloranil	0/3
2	2 ^a	<i>p</i> -chloranil	0/7
3	6 ^b	<i>p</i> -chloranil	2/12
4	38 ^c	DDQ ^d	5/nd

Table II.3: Initial optimization of C₃F₇ methyl ester synthesis. a: benzoate added after 30 min. b: benzoate added after 2 hours. c: benzoate added after 18 hours. d: added in 2, 1 equiv portions. First to reaction mixture for 18 hours then to filtrate dissolved in toluene, refluxed for 48 hours.

conditions, the desired product was isolated, however in low yield. Finally, lengthening the reaction time and changing the oxidant to DDQ doubled the yield to 5%.

The yields of porphyrin syntheses are typically quite low but 5% yield was unacceptable for generating the amount of porphyrin required to continue with the tweezer synthesis. Therefore, another route was desired. The synthesis of the desired porphyrin methyl ester was

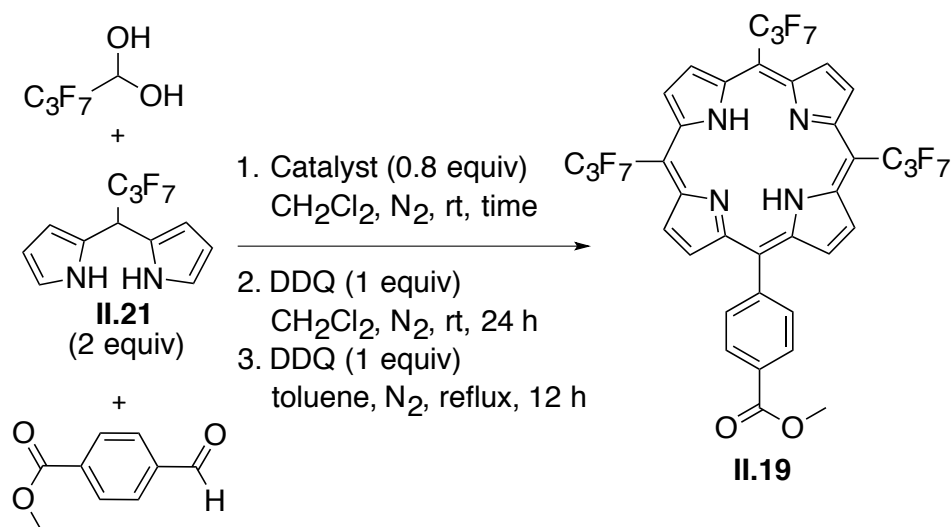


Entry	Catalyst	Solvent	Time (min)	Yield (%)
1	TFA	neat	15	0
2	InCl ₃	neat	15	0
3	HCl	THF	60	70 (21a)
4	HCl ^a	THF	60	43

Table II.4: Optimization of the C₃F₇ dipyrromethane synthesis. a: 20 equiv hydrochloric acid.

reported by Moore and coworkers in 2004.⁵³ Synthesis of the porphyrin methyl ester following this procedure required that the dipyrromethane of heptafluoropropylaldehyde hydrate (**II.21**) was first synthesized. Following the reported condensation with catalytic hydrochloric acid, alcohol **II.21a** was isolated in a 70% yield rather than the desired dipyrromethane. A screening of literature reported conditions for synthesis of dipyrromethanes was unsuccessful as both trifluoroacetic acid (TFA)⁵⁴ and indium (III) chloride (InCl₃)⁵⁵ failed (Table II.4). Eventually a 43% yield of the desired dipyrromethane was obtained when 20 equivalents of hydrochloric acid catalyst was used. Presumably, an excess of acid was necessary to promote the elimination of the hydroxyl group.

The dipyrromethane, heptafluoropropylaldehyde hydrate and 4-formyl methyl benzoate were then subjected to BF₃•OEt₂ catalyzed condensation and subsequent oxidation with DDQ for a total of 36 hours.⁵³ With this procedure, the methyl ester was obtained, however still at low yield (Table II.5). Improvement of the yield, was achieved when the dipyrromethane and

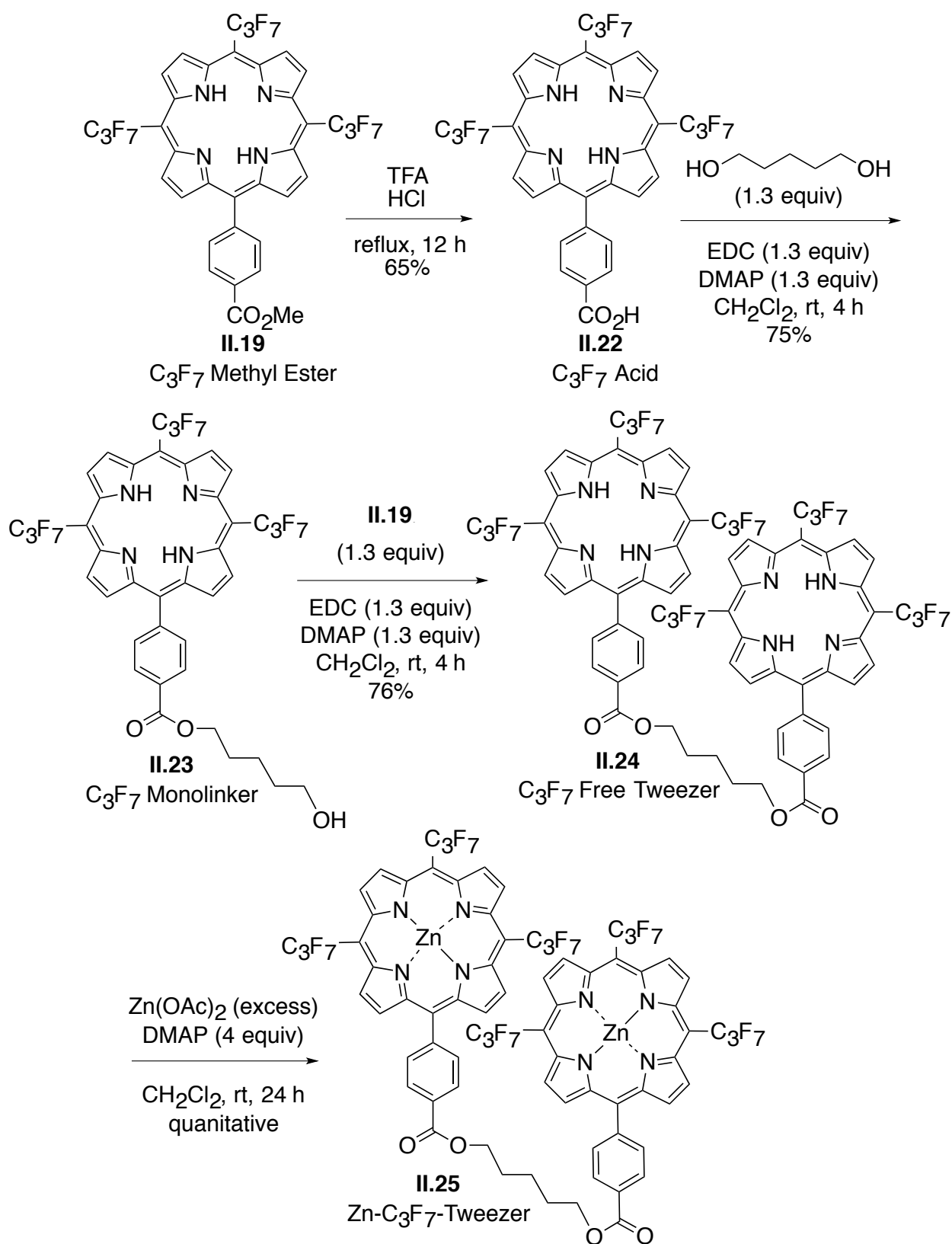


Entry	Time (h)	Catalyst	Yield %
1	19	$\text{BF}_3 \cdot \text{OEt}_2$	5
2	19 ^a	TFA	8
3	19 ^a	$\text{BF}_3 \cdot \text{OEt}_2$	15

Table II.5: Final optimization of the C_3F_7 methyl ester (**II.16**) synthesis. a: benzoate added after 3 hours.

perfluoropropyl hydrate were subjected to condensation for 4 hours prior to addition of the benzoate. Finally, switching the catalyst from $\text{BF}_3 \cdot \text{OEt}_2$ to TFA yielded the porphyrin methyl ester at a 15% yield which is an improvement over the literature reported 6% yield.⁵³

Scheme II.8 summarizes the completion of the synthesis of Zn- C_3F_7 -Tweezer (**II.25**). Pleased with the synthesis of **II.19**, the hydrolysis of the ester to provide C_3F_7 acid (**II.22**) was achieved under acidic conditions. To assemble the C_3F_7 monolinker (**II.23**), initially an attempt to convert the porphyrin acid to the porphyrin acyl chloride followed by addition of 1,5-pentane diol was pursued as there was literature precedence for synthesis of the porphyrin acyl chloride.⁵³ Unfortunately, decomposition of the porphyrin occurred. Alternatively, the EDC



Scheme II.8: Synthesis of the Zn- C_3F_7 -Tweezer (**II.25**).

catalyzed coupling sequence was used. Coupling of the **II.22** and 1,5-pentane diol provided **II.23** and the subsequent coupling of the **II.22** with **II.23** gave the C₃F₇ Free Tweezer (**II.24**) in 57% yield for the two steps. The zincation of the free tweezer gave quantitative yield of the Zn-C₃F₇-Tweezer (**II.25**).

II.5: Comparative ECCD Study Using the Perfluoroalkyl Porphyrin Tweezer

With the Zn-C₃F₇-Tweezer (**II.25**) in hand, an ECCD study of chiral diamines, amino alcohols and diols with the Zn-C₃F₇-Tweezer, Zn-TPFP-Tweezer and Zn-TPP-Tweezer was undertaken. If the *meso* phenyl substituents of the porphyrin are required for efficient chirality recognition, the ECCD amplitudes with Zn-C₃F₇-Tweezer should be consistently smaller than Zn-TPFP-Tweezer or Zn-TPP-Tweezer. Also, if the tighter binding is the result of the LUMO energies of the zinc center of the porphyrins, the calculated binding constants for any given substrate with Zn-C₃F₇-Tweezer should be smaller than Zn-TPFP-Tweezer or Zn-TPP-Tweezer.

The spectrophotometric analysis began by determining the absorption maximum and the extinction coefficient for the Zn-C₃F₇-Tweezer. This measurement was conducted in various solvents (Table II.6). In hexanes, the solvent used for the ECCD study, the tweezer had a λ_{max} of 409 nm and an extinction coefficient of 310,000 L mol⁻¹ cm⁻¹ in hexanes. The 5,10,15,20-tetrakis(heptafluoropropyl)porphyrin is reported to have a λ_{max} of 405nm and an extinction coefficient of 120,000 L mol⁻¹ cm⁻¹ in dichloromethane.⁵⁶ Also, prior to ECCD analysis of the substrate-tweezer complexes, UV-Vis titrations of the Zn-C₃F₇-Methyl ester with *sec*-butylamine and *tert*-butylalcohol were carried out. These UV-Vis titrations provide binding constants for amines and alcohols with the porphyrin monomer and provide the maximum

Solvent	λ_{max} (nm)	ϵ (L M ⁻¹ cm ⁻¹)
Hexanes	409	310,000
MCH	413	420,000
Toluene	417	530,000
CH ₂ Cl ₂	414	430,000
MeOH	415	290,000

Table II.6: Summary of UV-Vis data for the Zn-C₃F₇-Tweezer. All measurements 10⁻⁶ M, room temperature.

absorbance shift of the porphyrin when the substrate is bound. The λ_{max} shift values are important for comparison with the tweezer complexes. When a substrate binds to the metal center of a metalloporphyrin, the donation of electron density causes a red shift of the λ_{max} for the porphyrin. For example, the binding of sec-butyl amine to Zn-TPP-Methyl Ester causes a 12 nm red shift of the absorbance (Figure II.9 A). For a substrate-tweezer complex the observed λ_{max} shift is the result of two factors.⁵⁷ First, the donation of electron density from the substrate to the zinc centers of the porphyrins cause a red shift. However, there is a competing blue shift caused by the proximity of the porphyrins. When the complex forms, the porphyrins are brought close to one another to bind to the functional groups of the substrate. Bringing the porphyrins close to each other causes a blue shift that negates a portion of the red shift from the donation of electrons to the metal centers. Overall, a red shift is observed for the substrate-tweezer complexes as compared to the tweezer alone. It is expected that the λ_{max} of the substrate-methyl ester complex will red-shift more than the λ_{max} for the substrate-tweezer complex as the methyl ester complex will not have the competing blue shift. When the λ_{max} of

a substrate-tweezer complex is near that of the substrate-methyl ester complex, a 2:1 complex is suspected (Figure II.9 B).

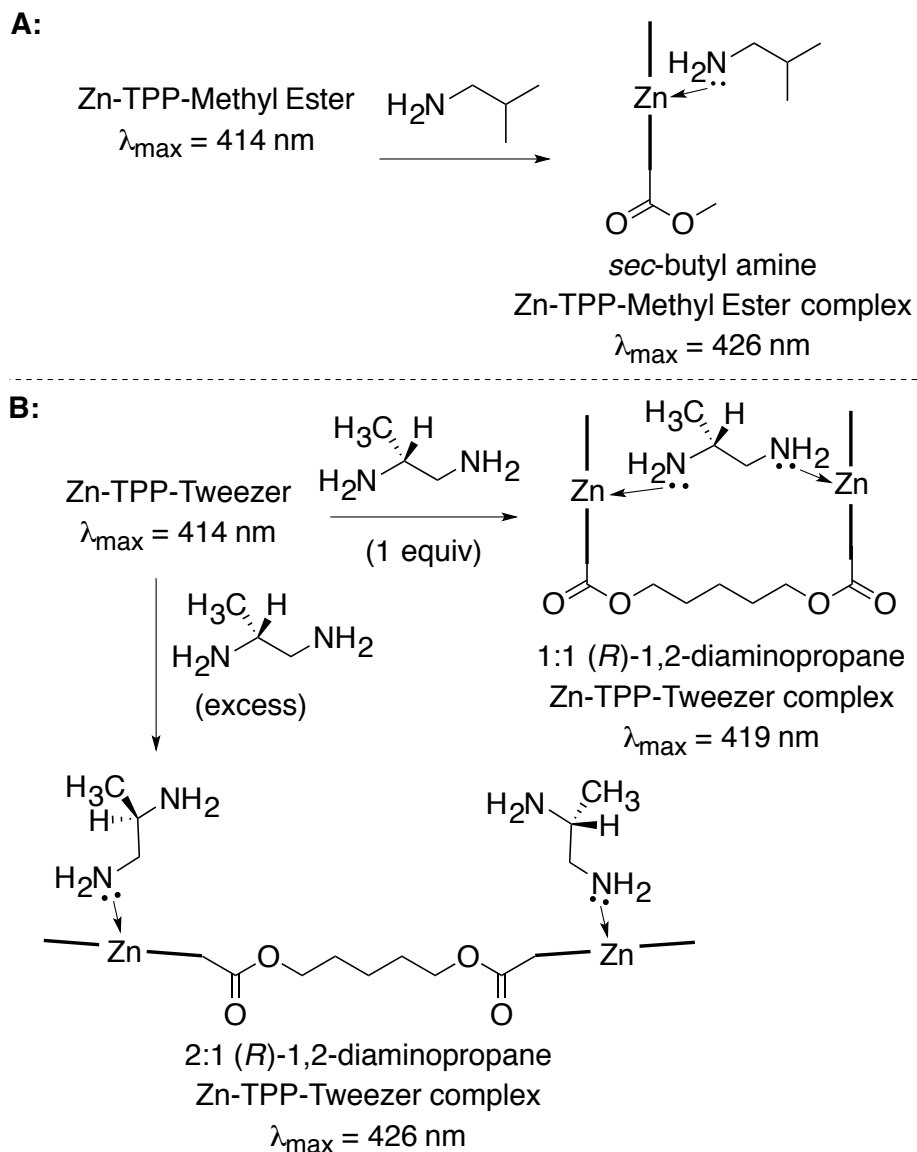


Figure II.9: Summary of the absorbance shifts for different substrate-porphyrin complexes. **A:** Binding of an amine to Zn-TPP-Methyl Ester causes a 12 nm red shift. **B:** 1:1 binding of a diamine to Zn-TPP-Tweezer causes a smaller red shift (8 nm) than the 2:1 binding (12 nm) due to the competing blue shift caused by the proximity of the porphyrins in the 1:1 complex.

Subjecting C₃F₇ Methyl ester (**II.19**) to zinc II acetate and DMAP provided the Zn-C₃F₇-Methyl Ester (**II.26**). UV-Vis monitored titration of Zn-C₃F₇-Methyl Ester with *sec*-butylamine and *tert*-butylalcohol was conducted. Addition of the *sec*-butylamine caused a 17 nm shift of the and addition of *tert*-butylalcohol caused a 7 nm shift. The UV-Vis was manipulated for determination of binding constants (see experimental for UV-Vis titration and binding constant determination graphs). The binding constant determined was in excess of 10⁶ M. An accurate value could not be calculated due to the poor fit of the equation. These large binding constants support the hypothesis that highly electron withdrawing substituents promote tight porphyrin-substrate binding.

The ECCD study began with the analysis of five chiral diamines with all three tweezers. The data is summarized in Table II.7. The ECCD data is reported as the wavelength of the Cotton effect with the amplitude of that Cotton effect in parenthesis. By convention, the first Cotton effect is the more red shifted signal and is listed first followed by the second Cotton effect and then the overall amplitude of the signal. The expected sign, determined from a previously established mnemonic,⁵ for each substrate is provided along with a Newman projection to explain the expected sign. For each substrate, the small group is highlighted in red and the large group in blue. When the porphyrin is bound to the chiral center, it will rotate toward the small group to reduce steric interactions. The second porphyrin will bind opposite the location of the first porphyrin leading to a helical arrangement. The bold arrow above the Newman indicates the helicity of the porphyrins once the substrate has bound to the tweezer and the positive or negative sign above the arrow indicates the expected sign. For every substrate-tweezer combination, the ECCD signal matched the expected sign. Furthermore,

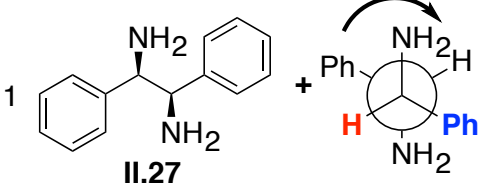
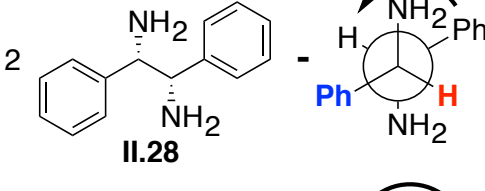
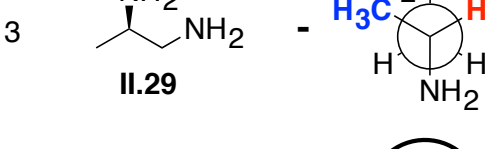
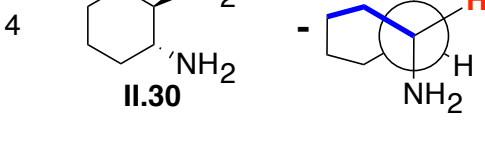
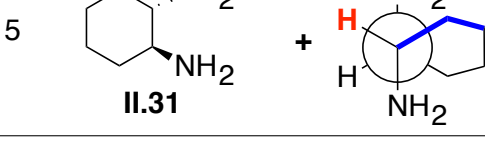
Entry	Chiral Diamine	Expected Sign	Zn-C ₃ F ₇ -Tz λ nm, ($\Delta\epsilon$)	Zn-TPFP-Tz λ nm, ($\Delta\epsilon$)	Zn-TPP-Tz λ nm, ($\Delta\epsilon$)
1	 II.27	+	426 (+64) 413 (-38) A = +102	430 (+209) 417 (-137) A = +346	431 (+211) 420 (-151) A = +362
2	 II.28	-	426 (-66) 414 (+42) A = -108	429 (-197) 417 (+158) A = -355	431 (-243) 417 (+181) A = -424
3	 II.29	-	427 (-82) 413 (+47) A = -129	427 (-294) 414 (+224) A = -518	432 (-132) 417 (+138) A = -270
4	 II.30	-	432 (-111) 416 (+112) A = -223	430 (-407) 416 (+337) A = -744	434 (-242) 419 (+274) A = -316
5	 II.31	+	431 (+151) 417 (-135) A = +286	429 (+353) 416 (-308) A = +661	434 (+271) 419 (-287) A = +358

Table II.7: Summary of the ECCD data for diamines. All measurements: hexanes, 0 °C, 2×10^{-6} M tweezer, 1 equivalent diamine.

enantiomers of a single chiral amine provided ECCD signals with opposite signs. Figure II.10 is an overlay of the ECCD curves for the enantiomers of 1,2-diaminocyclohexane with each of the tweezers. As expected the amplitudes observed with Zn-C₃F₇-Tweezer were considerably smaller than with the other two tweezers.

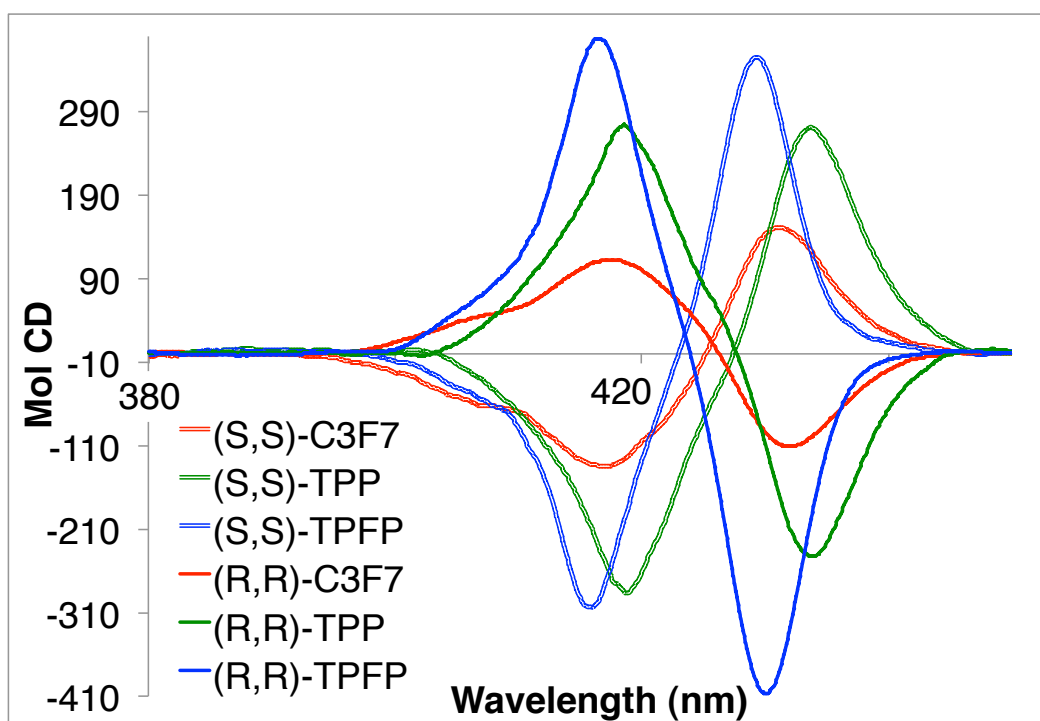


Figure II.10: Overlay of ECD spectra for 1,2-diaminocyclohexane with the Zn-Tweezers.

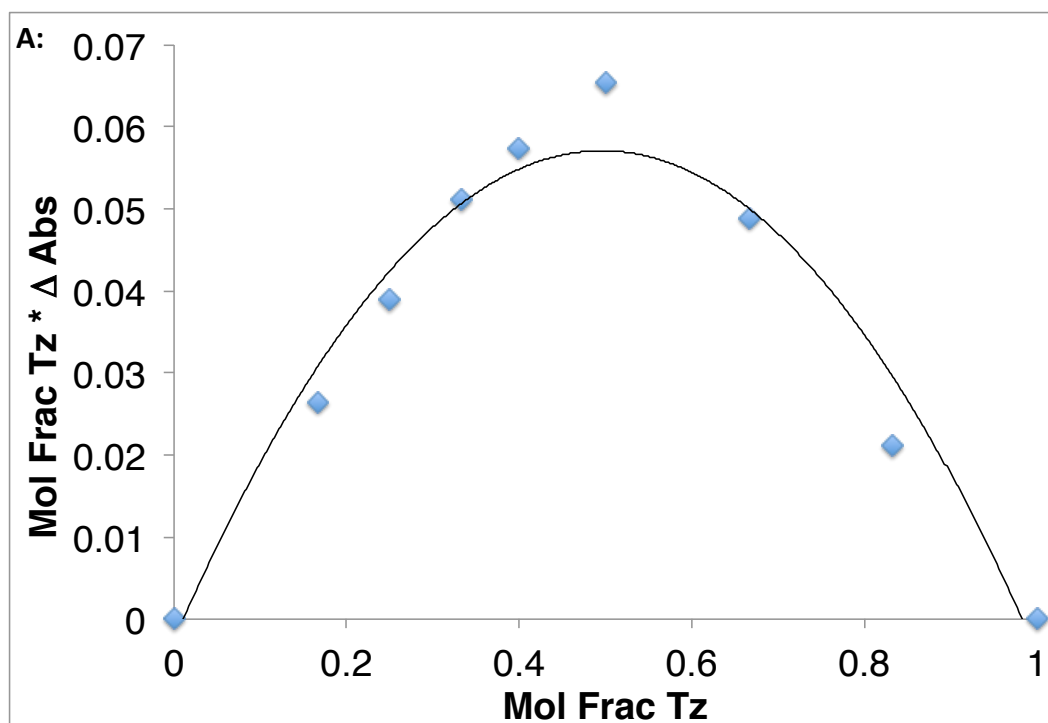
All measurements: hexanes, 0 °C, 2×10^{-6} M tweezer, 1 equivalent diamine.

Solvent and temperature screening with Zn-C₃F₇-Tweezer and 2*R*-diaminopropane was conducted to ensure that the optimal conditions were in use (Table II.8). Although, at room temperature the amplitude for this particular substrate was slightly larger, 0 °C was ultimately chosen as ECD amplitudes are known to decrease at room temperature for both Zn-TPFP-Tweezer and Zn-TPP-Tweezer.^{18,19} ECD amplitude in methylcyclohexane (MCH) was comparable to hexanes, however, the amplitudes were smaller and noisier in dichloromethane and toluene. Hexanes was chosen for the remainder of the study as Zn-TPFP-Tweezer¹⁹ and Zn-C₃F₇-Tweezer provide stronger signals in hexanes.

Solvent	Temp (°C)	Zn-C ₃ F ₇ -Tz λ nm, ($\Delta\epsilon$)
Hexanes	0	427 (-82) 413 (+47) A = -129
Hexanes	10	427 (-87) 415 (+53) A = -140
Hexanes	rt	427 (-101) 415 (+72) A = -173
MCH	0	428 (-63) 413 (+32) A = -95
Toluene	0	432 (-12) 415 (+10) A = -22 ^a
CH ₂ Cl ₂	0	426 (+14) 413 (-8) A = +22 ^a

Table II.8: Solvent and temperature screening of Zn-C₃F₇-Tweezer and (*R*)-2-diaminopropane. All measurements: 2x10⁻⁶ M tweezer, 1 equivalent diamine. a: 3 equivalents diamine.

In addition to the analysis by ECCD, each tweezer-substrate complex was analyzed by UV-Vis titration. As described above, the UV-Vis titration provides key information such as the type of complex formed (i.e. 1:1 or 2:1 substrate:tweezer) by Job's plot analysis^{58,59} and binding constants.⁶⁰ Both the Job's plot and the binding constant are found by comparison of the absorbance shift with the amount of substrate present. Figure II.11 provides the Job's plot and binding constant calculation for 1,2*R*-diaminopropane. The Job's plot correlates well with a 1:1 complex as the apex of the parabola is observed at a mol fraction of 0.5. A binding constant of 2x10⁷ M was calculated for this substrate. The binding constants for this diamine with Zn-TPP-Tweezer and Zn-TPFP-Tweezer were also calculated. Zn-TPP-Tweezer showed the smallest



B:

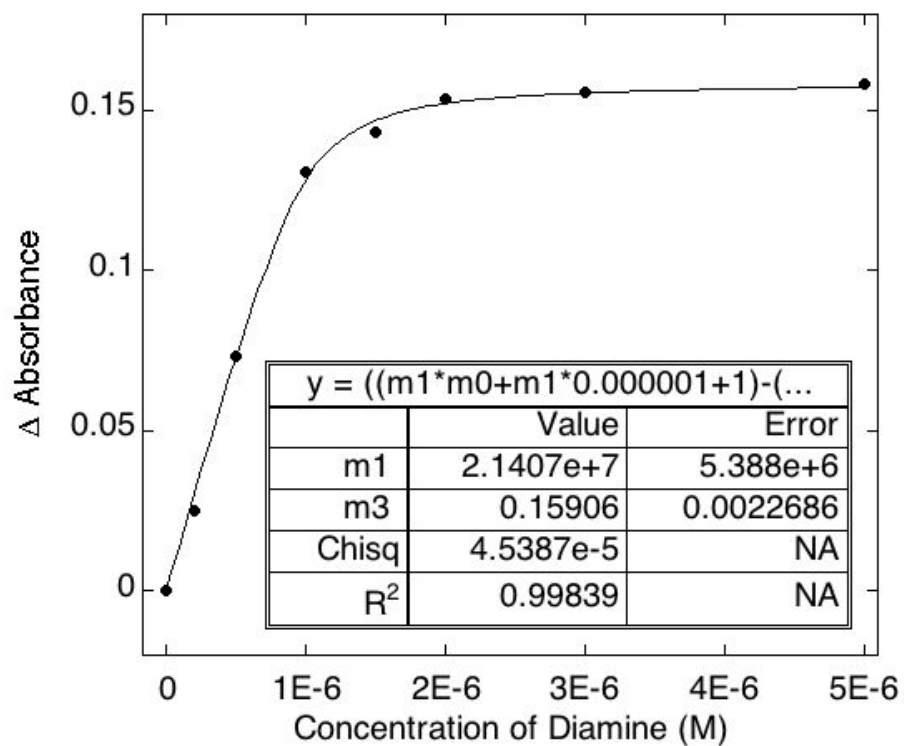


Figure II.11: Binding data for 1,2*R*-diaminopropane with Zn-C₃F₇-Tweezer. **A:** Job's plot indicating a 1:1 complex. **B:** The binding constant calculation.

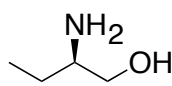
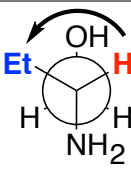
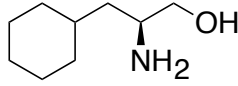
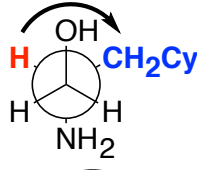
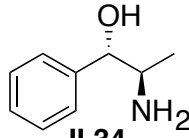
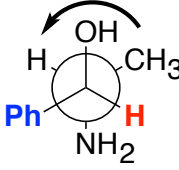
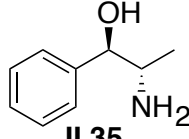
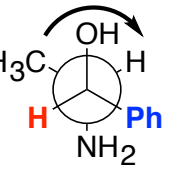
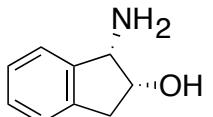
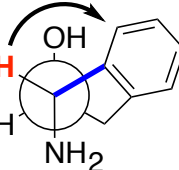
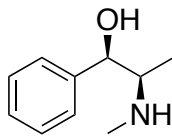
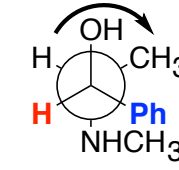
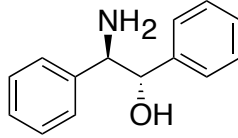
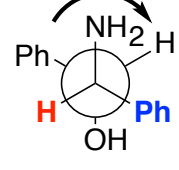
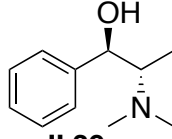
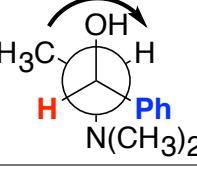
Entry	Chiral Amino Alcohol	Expected Sign	Zn-C ₃ F ₇ -Tz λ nm, ($\Delta\epsilon$)	Zn-TPFP-Tz λ nm, ($\Delta\epsilon$)	Zn-TPP-Tz λ nm, ($\Delta\epsilon$)
1	 II.32	- 	427 (-70) 411 (+52) A = -122	427 (-198) 413 (+136) A = -334	431 (-181) 417 (+159) A = -340
2	 II.33	+ 	428 (+115) 412 (-64) A = +179	427 (+256) 413 (-164) A = +420	432 (+296) 416 (-229) A = +535
3	 II.34	- 	424 (+12) 414 (-29) A = +41	423 (-255) 413 (+147) A = -402	427 (-91) 416 (+45) A = -136
4	 II.35	+ 	430 (-15) 415 (+52) A = -67	423 (+167) 413 (-80) A = +247	435 (-242) 427 (+56) 417 (-28)
5	 II.36	+ 	425 (+101) 414 (-47) A = +148 ^a	428 (+163) 419 (-126) A = +289 ^a	430 (+260) 421 (-190) A = +450 ^a
6	 II.37	+ 	428 (+25) 418 (-25) A = +50 ^a	430 (+63) 414 (-55) A = +118 ^a	432 (+52) 420 (-39) A = +91 ^a
7	 II.38	+ 	NO ECCD	428 (-14) 418 (+18) A = -32	429 (+154) 422 (-94) A = +248 ^b
8	 II.39	+ 	434 (-5) 423 (+21) 408 (-3)	423 (+17) 415 (-20) A = +37	430 (-82) 415 (+46) A = -128 ^c

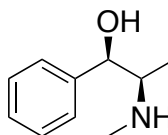
Table II.9: Summary of the ECCD data for amino alcohols. All measurements: hexanes, 0 °C, 2x10⁻⁶ M tweezer, 1 equivalent substrate. a: 40 equivalents amino alcohol. b: 75 equivalents substrate. c: 1500 equivalents amino alcohol.

binding constant at 5×10^5 M and binding affinity for Zn-TPFP-Tweezer was larger at 5×10^6 M. Surprisingly, the Zn-C₃F₇-Tweezer exhibited the largest binding constant. This was not expected as the E_{LUMO} energy of the Zn-C₃F₇-Tweezer was highest of the three tweezers.

Next a series of chiral amino alcohols were subjected to complexation with all three tweezers and both ECCD and UV-Vis titrations were conducted. The results are summarized in Table II.9. The expected ECCD signs are determined using the previously established mnemonic and are indicated by the positive or negative sign.¹⁹ The Newman projection is provided as rationalization for the observed sign. For these substrates, Zn-TPFP-Tweezer was the most consistent, providing an ECCD signal of the expected sign for every substrate tested. The results with Zn-TPP-Tweezer were a bit surprising as, the literature reported protocol for ECCD analysis of amino alcohols with Zn-TPP-Tweezer requires derivatization of the hydroxyl functionality prior to ECCD titration.⁵ But, for many substrates a robust signal was observed. However, for the (1*R*,2*S*)-norephedrine a complex ECCD signal was observed and the complex with (1*R*,2*S*)-*N*-methylephedrine provided a signal of the opposite sign predicted by the mnemonic. Therefore, Zn-TPP-Tweezer would not be reliable for the assignment of configuration of free amino alcohols.

The Zn-C₃F₇-Tweezer is the least successful of the three tweezers tested for the analysis of the amino alcohol substrates. As observed with the diamines, the ECCD amplitudes of the Zn-C₃F₇-Tweezer complexes were smaller than the signals observed with the other two tweezers. Furthermore, half of the substrates failed to follow the established mnemonic. The norephedrines showed ECCD signals with opposite signs as predicted by the mnemonic and the

**Binding Constants for
(*R,R*)-pseudoephedrine**



Tweezer	K_a (M^{-1})	Error	R^2
Zn- C_3F_7	2.1×10^5	6.2×10^3	0.99893
Zn-TPFP	2.7×10^5	1.7×10^4	0.99628
Zn-TPP	4.7×10^4	4.6×10^3	0.98733

Table II.10: Binding constants for (*1R,2R*)-psuedoephedrine with the tweezers.

more sterically demanding susbtrates, (*1S,2R*)-(+)-2-amino-1,2-diphenylethanol and (*1R,2S*)-*N*-methylephedrine, provided no ECCD signal and a complex signal, respectively.

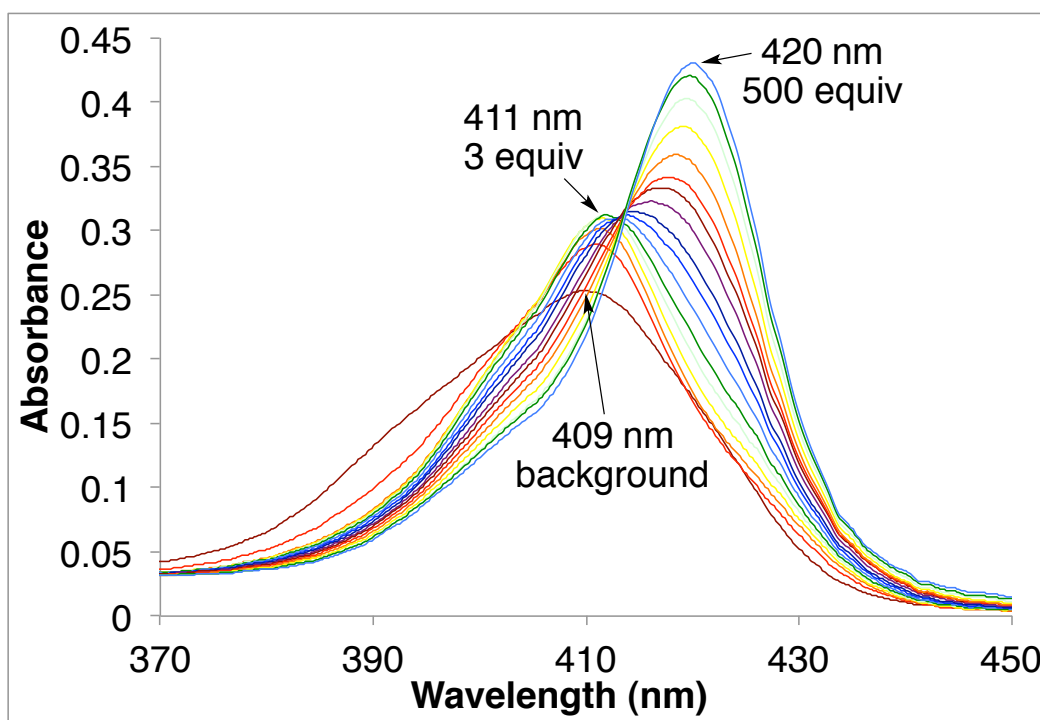


Figure II.12: UV-Vis titration of Zn- C_3F_7 -Tweezer with (*R*)-2-aminobutanol. Note that there is an initial Soret band shift to 411 nm with low equivalents of amino alcohol. The Soret band moves to 420 nm with excess amine. Spectra recorded in hexanes at room temperature.

The UV titrations of (1*R*,2*R*)-pseudoephedrine with the three tweezers indicate that the binding constant for with Zn-C₃F₇-Tweezer and Zn-TPFP-Tweezer are similar but Zn-TPP-Tweezer is approximately 10 fold smaller (Table II.10). For all three tweezers, the amine binding is considerably stronger than the hydroxyl thus, with an excess of amino alcohol present the 1:1 substrate-tweezer complex would break apart into a 2:1 substrate-tweezer complex resulting in a second red shift of the Soret band of the tweezer. Figure II.12 shows the UV-Vis titration of Zn-C₃F₇-Tweezer with (*R*)-2-aminobutanol. The porphyrin λ_{max} is observed at 409 nm. There is an initial shift to 411 nm at two equivalents of amino alcohol and with additional amino alcohol the Soret band shifts to an end point of 420 nm. The final absorbance is the same as the λ_{max} of the Zn-C₃F₇-Tweezer with *sec*-butylamine which indicates the 2:1 complex has formed (Figure II.9). The UV-Vis Soret shifts corresponding to the formation of the 2:1 was also observed for Zn-TPFP-Tweezer in this study and in the seminal Zn-TPFP-Tweezer report.¹⁹

Finally, the Zn-C₃F₇-Tweezer and the Zn-TPFP-Tweezer were used to evaluate a series of chiral diols (Table II.11). The Zn-TPP-Tweezer was omitted for the diol study. As described previously, the Zn-TPFP-Tweezer was designed for ECCD analysis of diols due to the lack of success with Zn-TPP-Tweezer.¹⁹ Again, the observed ECCD signals with Zn-C₃F₇-Tweezer were of smaller amplitudes than those observed with Zn-TPFP-Tweezer. In general, the Zn-C₃F₇-Tweezer did not provide reliable results. For four of the six diol complexes with Zn-C₃F₇-Tweezer, the ECCD signal was complex, unobservable or of the wrong sign. Surprisingly, the (2*S*,4*S*)-pentane diol gave an ECCD signal of the correct sign whereas, Zn-TPFP-Tweezer does not. The UV-Vis titrations of the diols did reveal that the binding constant for the diols are very

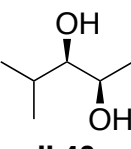
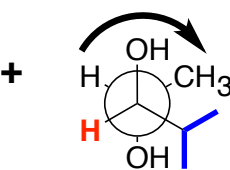
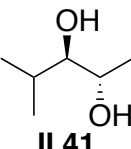
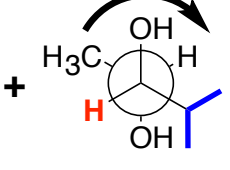
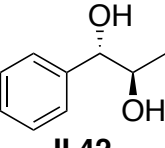
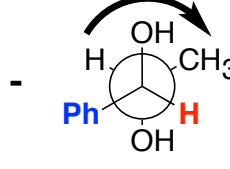
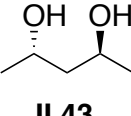
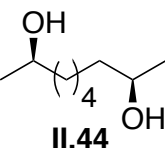
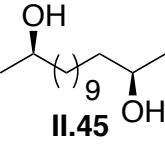
Entry	Chiral Diol	Expected Sign	Zn-C ₃ F ₇ -Tz λ nm, (Δε)	Zn-TPFP-Tz λ nm, (Δε)
1	 II.40		432 (-7) 419 (+32) 408 (-5) ^a A = +192	424 (+124) 412 (-68) A = +192
2	 II.41		418 (-8) 408 (+7) A = -15 ^b	421 (+33) 411 (-19) A = +52
3	 II.42		NO ECCD	421 (-38) 410 (+31) A = -69
4	 II.43	-	419 (-14) 405 (+8) A = -22	423 (+188) 413 (-105) A = +293
5	 II.44	+	420 (+95) 410 (-39) A = +134	423 (+222) 411 (-178) A = +400
6	 II.45	+	426 (-13) 419 (+180) 410 (-31)	429 (-165) 423 (+586) 412 (-123)

Table II.11: Summary of the ECCD data for diols. All measurements: hexanes, 0 °C, 2x10⁻⁶ M tweezer, 40 equivalents diol. a: 20 equivalents diol. b: 60 equivalents diol.

similar for Zn-C₃F₇-Tweezer and Zn-TPFP-Tweezer. The binding constant for the (1*R*,12*R*)-tetradecane diol with both tweezers was approximately 2x10⁵ M.

These results indicate, as hypothesized, that the Zn-C₃F₇-Tweezer is not reliable for ECCD evaluation of chiral substrates. There are however, several possible explanations for the

weaker ECCD signals observed with the Zn-C₃F₇-Tweezer complexes namely, weaker binding constants due to the higher LUMO energy of the zinc core of the porphyrin, smaller extinction coefficient of the porphyrin and reduced steric discrimination. First, the smaller signals could be a result of weaker binding constants. Weaker binding constants result in weaker substrate-tweezer complexes that could access a greater number of ECCD active complexes. This would cause the smaller amplitudes of the observed signal. The unreliable ECCD results for chiral diols and Zn-TPP-Tweezer is thought to be a result of weak binding.¹⁹ This is not considered a major factor as the binding constants for the Zn-C₃F₇-Tweezer and the Zn-TPFP-Tweezer are similar even though the LUMO energy is higher. The unexpectedly high binding constants with the Zn-C₃F₇-Tweezer could be due to the highly flexible nature of the alkyl *meso* substituents. Unlike phenyl substituents, alkyl chains can rotate out of the tweezer binding pocket. This will reduce steric interactions with the substrate as well as reducing porphyrin-porphyrin steric interactions. Reduced porphyrin-porphyrin steric interactions would allow for greater interaction with the substrate as the porphyrins can come in closer proximity to each other.

Secondly, the extinction coefficient of the chromophore was considered as the cause of the smaller ECCD amplitudes as, by definition, the ECCD amplitudes are proportional to the ϵ of the chromophore.^{2,3} The ϵ of Zn-C₃F₇-Tweezer ($\epsilon = 310,000 \text{ L mol}^{-1} \text{ cm}^{-1}$ in hexanes) is approximately a third of the ϵ of Zn-TPFP-Tweezer ($\epsilon = 980,000 \text{ L mol}^{-1} \text{ cm}^{-1}$ in hexanes) and in all cases the ECCD amplitudes are smaller with Zn-C₃F₇-Tweezer. However, this was eliminated as the major contributing factor to the unreliability of Zn-C₃F₇-Tweezer. The ϵ of Zn-TPP-Tweezer ($\epsilon = 440,000 \text{ L mol}^{-1} \text{ cm}^{-1}$ in hexanes) is similar to Zn-C₃F₇-Tweezer ($\epsilon = 310,000 \text{ L mol}^{-1} \text{ cm}^{-1}$ in hexanes) and yet the ECCD amplitudes of the diamine complexes are much larger

for the Zn-TPP-Tweezer. If the smaller ϵ was the only reason for the smaller amplitudes, these two tweezers should have similar ECCD amplitudes. Additionally, the smaller ϵ does not explain the cases in which the ECCD signal was unobservable, complex or of the incorrect sign.

The single greatest factor leading to the smaller amplitudes is the inefficient transfer of chirality from the substrate to the tweezer. This is caused by the reduced interactions between the substituents at the *meso* positions of the porphyrins and the chiral center(s) of the substrate. As hypothesized, these flexible alkyl chains rotate out of the binding pocket to minimize the steric interactions. This hypothesis was further confirmed by computation. Shown in Figure II.13 are energy minimized structures for the complexes of Zn-TPFP-Tweezer (**A**) and Zn-C₃F₇-Tweezer (**B**) with (*S*)-1,2-diaminopropane. In black are the distances between the *meso* substituent of the porphyrin and the methyl of the amine chiral center. As

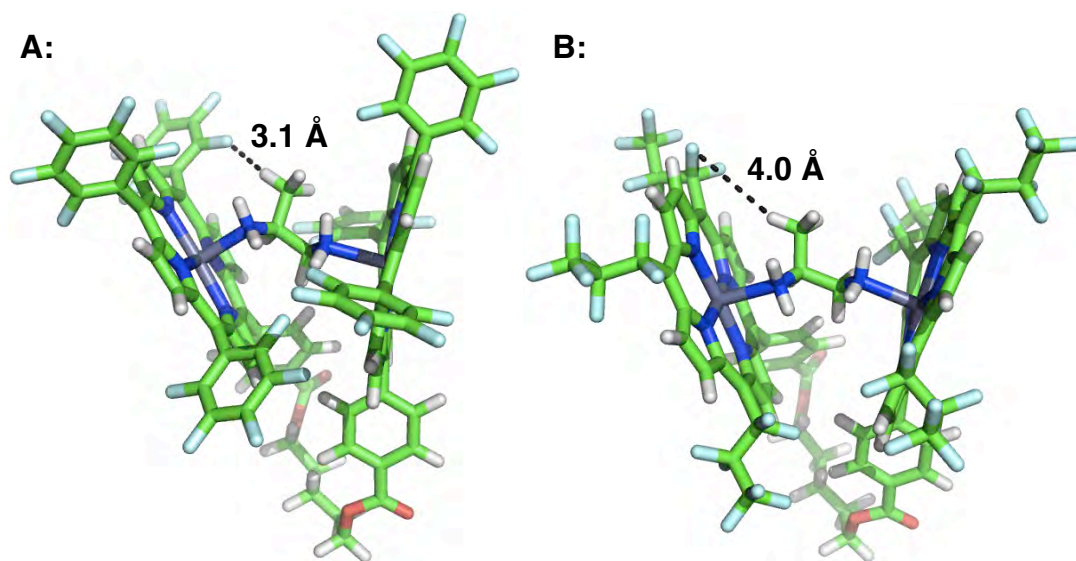


Figure II.13: Energy minimized structures of Zn-TPFP-Tweezer (**A**) and Zn-C₃F₇-Tweezer (**B**) with (*S*)-1,2-diaminopropane.

hypothesized, the distance is greater for the Zn-C₃F₇-Tweezer therefore, there is reduced steric discrimination and smaller ECCD amplitudes with this tweezer.

II.6: Conclusions

The results of this study confirmed the correlation of increased Lewis acidity of the zinc center of the porphyrin and the increase in substrate binding constants. The highly fluorinated tweezers, Zn-C₃F₇-Tweezer and Zn-TPFP-Tweezer were shown to have similar LUMO energies and similar substrate binding constants. Also, the results of this study were instrumental in showing the necessity of the *meso* phenyl substituents for efficient transfer of chirality from the substrate to the tweezer. Calculation confirmed that the flexible alkyl chains of the Zn-C₃F₇-

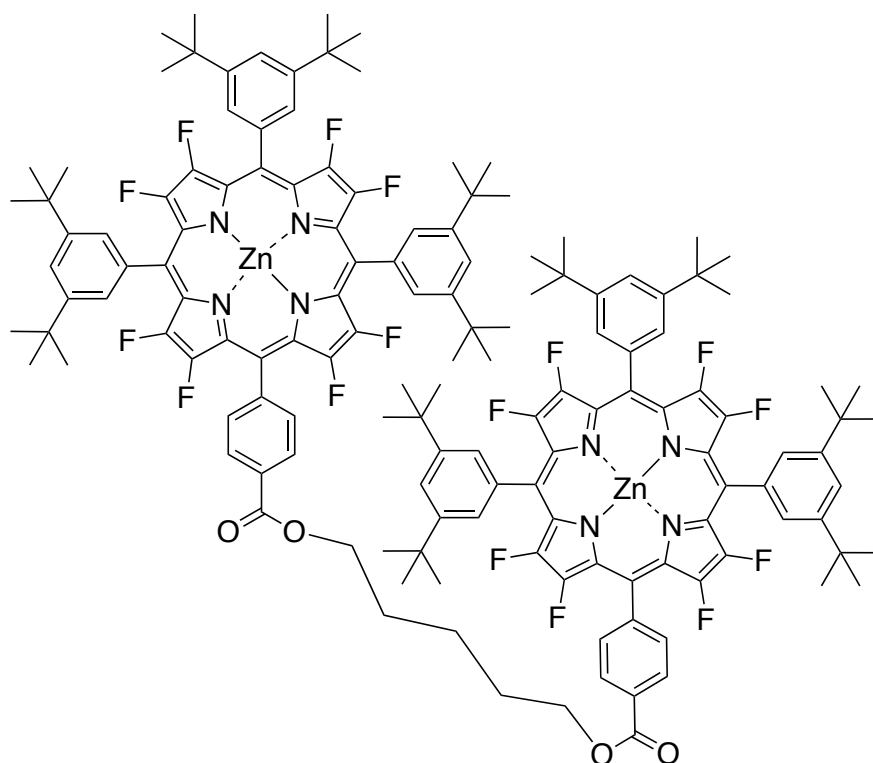


Figure II.14: The proposed “super-tweezer” for future ECCD studies.

Tweezer rotate to minimize interaction with the substrate and as a result, weaker ECCD signals are observed. Future work should be directed toward synthesis of another of the proposed “super-tweezers” namely the electron-deficient tweezer featuring difluoropyrrole to incorporate the electron withdrawing groups and *tert*-butylphenyl substituents of the Zn-TBP-Tweezer to promote rotation of the porphyrins (methyl ester shown in Figure II.14). This tweezer would have the benefit of the Lewis acidic zinc and the steric interactions to force a larger angle between the porphyrins. This tweezer should have the substrate scope of Zn-TPFP-Tweezer and the large amplitudes of the Zn-TBP-Tweezer.

II.7: Experimental Procedures

II.7.1: General Procedures

Where it is stated that dry CH_2Cl_2 or dry toluene was used, the solvent was distilled over CaH_2 . Dry THF and diethyl ether were obtained by distillation from sodium benzophenone ketyl. All other reagents, unless indicated otherwise, were purchased from commercial sources.

Thin layer chromatography was performed on Merck aluminum sheets coated with silica gel (0.2 mm thickness). Potassium permanganate, anisaldehyde, polymolybdic acid and UV were used for visualization. Silica chromatography was performed using Dynamic Adsorbents Inc Flash Silica Gel 32-634.

^1H NMR was recorded with Varian Inova 300 or 500 MHz instruments in CDCl_3 . The reported ^1H NMR chemical shifts are relative to the CDCl_3 line (7.24 ppm) and the ^{13}C NMR chemical shifts are relative to the central CDCl_3 line (77.0 ppm). ^{19}F NMR was recorded on the 300 MHz instrument. Mass spectra were recorded on a micromass VG-70 mass spectrometer. UV-Vis spectra were recorded on a Perkin-Elmer Lambda 40 spectrophotometer. The CD spectra were recorded on a Jasco J-810 spectropolarimeter equipped with a Neslab 111 temperature controller.

II.7.2: General Procedure for ECCD Measurement

To hexanes (1 mL) in a 1.0 cm cell, 2 μL of a 1 mM stock solution of zinc porphyrin tweezer (C5-Zn-TPFP-Tz) in anhydrous CH_2Cl_2 was added to provide a 2 μM tweezer solution. The background spectrum was recorded from 380 nm to 450 nm at a scan rate of 50 nm/min at

the specified temperature. Each chiral guest molecule was dissolved in anhydrous CH_2Cl_2 to afford a 1 mM solution then 0.2 to 100 μL of this solution was added to the cell with the tweezer solution affording the host-guest complex. For substrates that required high concentration of guest, a 10 mM solution in anhydrous CH_2Cl_2 was prepared then 1 to 100 μL of this solution was added to the cell with the tweezer solution. The ECCD spectra was immediately recorded following addition of the guest solution (minimum of 4 accumulations). The resultant ECCD spectra, which is reported in millidegrees, was normalized to the tweezer concentration to obtain molecular CD (Mol CD).

II.7.3: General Procedures for UV-Vis Measurement, Job's Plot Analysis, and Binding Constant Determination

To hexanes (1 mL) in a 1.0 cm cell, 1 μL of a 1 mM stock solution of zinc porphyrin tweezer (C5-Zn-TPFP-Tz) in anhydrous CH_2Cl_2 was added to provide a 1 μM tweezer solution. The background spectrum was recorded from 600 nm to 350 nm at a scan rate of 240 nm/min at room temperature. Each chiral guest molecule was dissolved in anhydrous CH_2Cl_2 to afford a 1 mM solution then 0.2 to 100 μL of this solution was added to the cell with the tweezer solution affording the host-guest complex. For substrates that required high concentration of guest, a 10 mM solution in anhydrous CH_2Cl_2 was prepared then 1 to 100 μL of this solution was added to the cell with the tweezer solution. The UV-Vis spectrum was collected immediately after addition of the guest solution.

The UV-Vis measurements were manipulated for the purpose of determining the complex stoichiometry by Job's plot analysis. First, the molar fraction of tweezer in the solution

was first determined by dividing the moles of tweezer by the total number of moles (moles of tweezer and moles of guest molecule) present in solution. Second, the change in absorbance with each addition of guest molecule was determined. The molar fraction of tweezer and the change of absorbance were multiplied together. The Job's plot was generated by plotting molar fraction tweezer versus molar fraction tweezer multiplied by change in absorbance in Excel. A parabolic curve is generated and the apex of the parabola provides the molar fraction of tweezer in the host-guest complex. A 1:1 complex is formed when the apex falls at a molar fraction of 0.5.

The UV-Vis measurements were manipulated for the purpose of determining the binding affinity of the guest molecule for the tweezer. The concentration of the guest molecule was determined based on the equivalents of the guest added to the tweezer solution. Also, the change of absorbance for each addition of the guest was determined. Using, KaleidaGraph a plot of the concentration of guest versus the change in absorbance was generated and a line of best fit was calculated based on the following equation:

$$F = F_0 - \frac{1 + (P_T + R_T)K_a - \sqrt{(P_T - R_T)^2 K_a^2 + 2(P_T + R_T)K_a + 1}}{2(P_T K_a)} (F_0 - F_\infty)$$

F = absorbance of the tweezer at a given concentration of guest.

F₀ = absorbance of the tweezer without guest.

F_∞ = absorbance of the tweezer at saturation with the guest.

P_T = concentration of the tweezer.

R_T = concentration of the guest molecule.

K_a = binding constant.

Substrates II.27 - II.39 were purchased from Sigma-Aldrich. Substrates II.40 - II.45 were synthesized by Dr. Xiaoyong Li. The synthesis of these molecules were reported in his thesis.

II.7.4: Synthesis and Characterization Data for Substrates

Dipyrromethane (II.1):⁴ Pyrrole (100 mL, 1.44 mol, 25 equiv) and paraformaldehyde (1.73 g, 57.7 mmol, 1 equiv) were added to a 500 mL 3 neck flask that was equipped with N₂ adaptor, thermometer and a reflux condenser. While stirring under N₂, the contents were heated to 50 °C. The heating mantle was removed and TFA (450 μ L, 5.77 mmol, 0.1 equiv) was added. The mixture was then heated to 90 °C and stirred for 15 minutes. The heating mantle was removed and NaOH (0.1 M, 3 mL) was added to quench and the contents were stirred for an additional 1 hour. The contents of the flask and EtOAc (50 mL) were added to a 500 mL separatory funnel. The organic layer was washed with de-ionized water (200 mL, 2 xs) then the organic layer was dried with Na₂SO₄. The solution was condensed under reduced pressure and the dark oil was purified via silica chromatography (15% EtOAc/hexane) to afford **1** (2.5 g, 30%) as a yellow solid. (II.1): ¹H NMR (CDCl₃, 300 MHz): δ 7.66 (2H, s), 6.61-6.59 (2H, m, J = 2.7 Hz, 4.2 Hz), 6.17-6.14 (2H, dd, J = 2.7 Hz, 5.4 Hz), 6.05-6.03 (2H, m), 3.92 (2H, s).

¹³C NMR (CDCl₃, 125 MHz): δ 129.0, 117.3, 108.3, 106.4, 26.3

Mass Spectrum: [C₉H₁₀N₂]⁺ observed 146.1 m/z calculated 146.1 m/z

Melting Point: 70 - 73 °C

R_f: 0.8 (15% EtOAc/Hexanes)

5-(4-methylcarboxyphenyl)-porphyrin (**II.2**): Terephthalaldehydic acid methyl ester (330 mg, 2.00 mmol, 1 equiv), pyrrole-2-carboxaldehyde (380 mg, 4.00 mmol, 2 equiv) and dipyrrolemethane (300 mg, 2.00 mmol, 1 equiv) were dissolved in CH₂Cl₂ (1 L) in a 2 liter round-bottom flask which was covered with aluminum foil. The solution was stirred under N₂ for 10 minutes followed by addition of TFA (70 μ L, 0.9 mmol, 0.45 equiv). The solution then stirred for 16 hours. To the dark solution, *p*-chloranil (1.53 g, 5.73 mmol, 2.9 equiv) was added and stirring was continued for 1 hour followed by addition of Et₃N to quench. The mixture was stirred for another hour. The solution was concentrated under reduced pressure and the resulting black residue was purified by silica chromatography (50% CH₂Cl₂/hexane). The desired product (**II.2**, 0.044 g, 4.3%) was obtained as a burgundy solid.

(**II.2**): ¹H NMR (CDCl₃, 300 MHz): δ 10.34 (2H, s), 10.28 (1H, s), 9.51-9.47 (4H, dd, *J* = 4.8, 7.2 Hz), 9.42 (2H, d, *J* = 4.5 Hz), 9.27 (2H, d, *J* = 4.5 Hz), 8.47 (2H, d, *J* = 8.4 Hz), 8.33 (2H, d, *J* = 8.7 Hz), 4.12 (3H, s).

Mass Spectrum: [C₂₉H₂₁N₄O₂]⁺ observed 445.2 m/z calculated 445.17 m/z

Melting Point: 125 - 130 °C

R_f: 0.75 (100% CH₂Cl₂)

Unsubstituted Porphyrin Acid (**II.3**): In a 25 mL round bottom flask, 5-(4-methylcarboxyphenyl)-porphyrin (**II.2**, 75 mg, 0.15 mmol) was dissolved in THF (15 mL) and NaOH (aq, 2 M, 15 mL). The methyl ester was soluble in the THF and insoluble in the NaOH. The mixture was refluxed overnight (~12 hours) and quenched when the water layer was red, indicating that the acid had formed. The THF was removed under reduced pressure and the basic aqueous layer was

quenched with HCl (aq, 3 M). Extraction of the water layer was attempted with diethyl ether, CH₂Cl₂, EtOAc, toluene, and hexanes. Extraction of limited amounts of the acid could be achieved with EtOAc. Removal of the solvent under reduced pressure gave the porphyrin acid as a red solid (II.3, 10 mg, 16%).

(II.3): ¹H NMR (CDCl₃/CD₃OD, 300 MHz): δ 10.24 (2 H, s), 10.81 (1 H, s), 9.85 (4 H, m), 9.31 (2 H, d, *J* = 4.8 Hz), 8.92 (2 H, d, *J* = 4.5 Hz), 8.36 (2 H, d, *J* = 8.1 Hz), 8.21 (2 H, d, *J* = 8.1 Hz)

Mass Spectrum: [C₂₇H₁₉N₄O₂]⁺ observed 431.0 m/z calculated 431.15 m/z

Melting Point: 115 - 120 °C

R_f: 0.15 (10% MeOH/CH₂Cl₂)

Unsubstituted Porphyrin Monolinker (II.4): A. EDC Coupling: Unsubstituted porphyrin acid (II.3, 75 mg, 0.17 mmol, 1 equiv) was dissolved in dry CH₂Cl₂ (17 mL) in a flame dried, 50 mL round bottom flask while stirring. To the flask, 1,5-pentanediol (0.03 mL, 30 mg, 0.23 mmol, 1.3 equiv), DMAP (28.1 mg, 0.23 mmol, 1.3 equiv) and EDC (0.23 mmol, 1.3 equiv) were added. The solution stirred for 12 hours and then solvent was removed under reduced pressure to give the crude product. This was purified via column chromatography (50% CH₂Cl₂/hexane-100% CH₂Cl₂) to give the desired product (8 mg, 10%) as a red solid.

B. Iodine Catalyzed Transesterification of the Porphyrin Methyl Ester: The unsubstituted porphyrin methyl ester (II.2, 20 mg, 0.05 mmol, 1 equiv), 1,5-pentanediol (0.5 mL, large excess) and iodine (152.2 mg, 0.6 mmol, 12 equiv) were added to a 5 mL round bottom flask then refluxed while stirring under N₂ for 36 hours. No product was obtained based on NMR.

C. Acid Catalyzed Transesterification of the Porphyrin Methyl Ester: To 50 mL pear shaped flask 1,5-pentanediol (1 mL, large excess), unsubstituted porphyrin methyl ester (II.2, 20 mg, 0.05 mmol, 1 equiv) and sulfuric acid (0.027 mL, 0.5 mmol, 10 equiv) were added. The mixture was heated to 55 °C for 18 hours while stirring. The reaction mixture was directly purified via column chromatography (50% CH₂Cl₂/hexane-100% CH₂Cl₂) to give the desired product as purple solid (30%).

D. Lewis Base Catalyzed Transesterification of the Benzyl Ester with DBU: The unsubstituted porphyrin benzyl ester (II.7, 52 mg, 0.1 mmol, 1 equiv) was dissolved in 1,5-pentane diol (0.5 mL) to which, lithium bromide (41 mg, 5 equiv) and DBU (7.7 µL, 0.5 equiv) were added. The reaction was stirred for 24 hours under N₂. There was no reaction by TLC.

E. Lewis Base Catalyzed Transesterification of the Benzyl Ester without DBU: The unsubstituted porphyrin benzyl ester (II.7, 52 mg, 0.1 mmol, 1 equiv) was dissolved in dry CH₂Cl₂ (0.5 mL) to which, 1,5-pentane diol (0.1 mL, 10 equiv) and lithium bromide (82 mg, 10 equiv) were added. The reaction was stirred for 24 hours under N₂. There was no reaction by TLC.

F. Unsubstituted Phenyl Ester Transesterification with Sodium Hydride: A 1 M solution of sodium hydride (NaH, 0.8 g, 20 mmol) was suspended in dry THF (20 mL) in a flame dried 100 mL flask under N₂ at room temperature. In a flame dried 25 mL round bottom flask under N₂ at room temperature, 1,5-pentane diol (0.5 mL, 0.495 g, 4 mmol) was dissolved in dry THF (3.5

mL). The NaH solution was added to the diol solution until bubbling ceased, approximately 0.5 mL (5 mmol) was added.

In a separate flame dried 25 mL flask, unsubstituted porphyrin phenyl ester (5 mg, 10 μ mol, 1 equiv) was dissolved in dry CH_2Cl_2 (3 mL) while stirring under N_2 at room temperature. The diol solution was transferred dropwise to the porphyrin solution. The mixture was stirred until gas evolution ceased. The reaction was then quenched with HCl (aq, 2M, 1 mL). The reaction was diluted with CH_2Cl_2 (20 mL) then washed with HCl (aq, 2 M, 10 mL, 2 xs), NaOH (aq, 2 M, 10 mL), water (10 mL, 3 xs) and NaCl (sat aq, 10 mL). The organic layer was then dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude was purified by column chromatography (10% EtOAc/ CH_2Cl_2) to give the desired product as a red solid (4.8 mg, 94%).

(II.4): ^1H NMR (CDCl_3 , 300 MHz): δ 10.34 (2H, s), 10.28 (2H, s), 9.48 (4H, dd, $J = 4.2, 6.9$ Hz), 9.41 (2H, d, $J = 4.5$ Hz), 9.03 (2H, d, $J = 4.8$ Hz), 8.47 (2H, d, $J = 7.8$ Hz), 8.33 (2H, d, $J = 7.8$ Hz) 4.59 (2H, t, $J = 7.0$ Hz), 3.79 (2H, t, $J = 4.5$ Hz), 2.01 (2H, quintet, $J = 5.0, 14.0$ Hz), 1.78 (2H, m), 1.72 (2H, m)

Mass Spectrum: $[\text{C}_{27}\text{H}_{18}\text{N}_4\text{O}_2]^+$ observed 516.2 m/z calculated 516.2 m/z

Melting Point: decomposition 260 $^\circ\text{C}$.

Rf: 0.5 (10% EtOAc/ CH_2Cl_2)

Unsubstituted Porphyrin Tweezer (**II.5**): A: EDC Coupling: To a flame dried 10 mL round bottom flask under N₂, unsubstituted porphyrin monolinker (3 mg, 5.8 μmol, 1 equiv), unsubstituted porphyrin acid (**II.3**, 3.25 mg, 7.5 μmol, 1.3 equiv), EDC (1.44 mg, 7.5 μmol, 1.3 equiv) and DMAP (0.92 mg, 7.5 μmol, 1.3 equiv) were dissolved in dry CH₂Cl₂ (1.5 mL). The reaction was monitored by TLC. After 24 hours, no reaction was observed, additional EDC (1.44 mg, 7.5 μmol, 1.3 equiv) and DMAP (0.92 mg, 7.5 μmol, 1.3 equiv) were added. The reaction was stirred another 24 hours. No reaction was observed. The starting materials were quantitatively isolated and the desired tweezer was not observed.

B: Acid chloride: To a flame dried 100 mL round bottom flask under N₂, the unsubstituted porphyrin acid (**II.3**, 25 mg, 0.034 mmol, 1 equiv) and pyridine (1 mL, 1.02 g, 13 mmol, 382 equiv) were dissolved in dry toluene. Then thionyl chloride (4 μL, 6.5 mg, 0.54 mmol, 1.6 equiv) was added. This mixture was stirred for 1 hour to generate the acid chloride. The solvent was then removed under reduced pressure. The crude acid chloride was then dissolved in dry toluene (5 mL) and pyridine (0.5 mL, 0.51 g, 6.5 mmol, 190 equiv) in a 50 mL round bottom flask under N₂. A separate solution of unsubstituted porphyrin monolinker (**II.4**, 18 mg, 0.034 mmol, 1 equiv) in dry toluene (15 mL) and pyridine (0.5 mL, 0.51 g, 6.5 mmol, 190 equiv). The monolinker solution was then added dropwise to the acid chloride solution. After 1 hour, the reaction was quenched with water (10 mL). The organic layer was washed with water (20 mL, 3 xs) and then dried with Na₂SO₄. The solvent was removed under reduced pressure. There was no reaction as evident by TLC and NMR. Only monolinker was observed by crude NMR indicating the porphyrin acid had possibly decomposed. The desired product was not obtained.

C: Acid Catalyzed Transesterification: To dry toluene (2 mL) in a 10 mL round bottom flask, was added unsubstituted porphyrin monolinker (II.4, 3 mg, 6 μ mol, 1 equiv), unsubstituted porphyrin methyl ester (II.2, 8 mg, 18 μ mol, 3 equiv) and sulfuric acid (0.1 mL) were added and the reaction was heated to 40 °C. After 4 hours, the reaction was quenched with water (2 mL). The organic was diluted with CH₂Cl₂ (10 mL) and was washed with water (5 mL, 3 xs). The organic was dried with Na₂SO₄ and the solvent was removed under reduced pressure. By crude NMR, the porphyrin methyl ester was recovered; the monolinker was not. The monolinker may have hydrolyzed to the acid as porphyrin was removed in the water layer during extraction. The tweezer was not obtained.

Benzyl 4-formylbenzoate (II.6):⁶¹ Terephthalaldehydic acid (2 g, 0.013 mol, 1 equiv), benzyl bromide (1.7 mL, 0.014 mol, 1.1 equiv), potassium carbonate (3.59 g, 0.028 mol, 2 equiv) and *t*-butylammonium iodide (0.48 g, 1.3 mmol, 0.1 equiv) were dissolved in dry THF (150 mL) in a 300 mL flame dried round bottom flask. The solution was stirred and refluxed for 48 hours under N₂. The solution was cooled to room temperature then diluted with CH₂Cl₂ (300 mL) and extracted with water (300 mL, 2 xs). The organic layer was dried with Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified using silica chromatography (20% EtOAc/hexane) to afford II.6 (3.05 g, 96%) as an orange oil. ¹H and ¹³C NMR match literature reported spectra.

(II.6): ¹H NMR (CDCl₃, 300 MHz): δ 10.08 (1H, s), 8.22 (2H, d, *J* = 8.4 Hz), 7.93 (2H, d, *J* = 8.4 Hz) 7.43-7.34 (5H, m), 5.38 (2H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 191.5, 165.3, 139.2, 135.5, 135.1, 130.3, 129.4, 128.6, 128.5, 128.3, 67.3

Mass Spectrum: $[\text{C}_{15}\text{H}_{12}\text{O}_3]^+$ observed 240.0 m/z calculated 240.1 m/z

Melting Point: 35 - 40 °C (142 - 144 °C Reported)

Rf: 0.55 (20% EtOAc/Hexanes)

5-(4-benzylcarboxyphenyl)-porphyrin (**II.7**): Dipyrromethane (**II.1**, 300 mg, 2.06 mmol, 1 equiv), pyrrole-2-carboxaldehyde (380 mg, 4.00 mmol, 1.94 equiv) and benzyl 4-formylbenzoate (500 mg, 2.06 mmol, 1 equiv) were dissolved in CH_2Cl_2 (600 mL) in a 3 liter, 3 neck flask that had been covered with aluminum foil. The solution was stirred under N_2 for 16 hours. Then *p*-chloranil (1.53 g, 5.73 mmol, 2.9 equiv) was added and the dark solution was stirred for an additional hour followed by the addition of Et_3N . The reaction was stirred for an additional hour. The solution was concentrated under reduced pressure and the resulting black residue was purified using silica chromatography (20-50% CH_2Cl_2 /hexane) to afford **II.7** (206 mg, 10%) as a red crystals.

(**II.7**): ^1H NMR (CDCl_3 , 300 MHz): δ 10.21 (2H, s), 10.13 (1H, s), 9.39-9.23 (6H, m), 8.98 (2H, d, J = 4.5 Hz), 8.52 (2H, d, J = 8.1 Hz), 8.30 (2H, d, J = 8.1 Hz), 7.66-7.44 (5H, m), 5.61 (2H, s), -3.79 (2H, br s).

Mass Spectrum: $[\text{C}_{34}\text{H}_{24}\text{N}_4\text{O}_2]^+$ observed 520.0 m/z calculated 520.2 m/z

Melting Point: decomposition 175 °C

Rf: 0.65 (100% CH_2Cl_2)

Hydrogenation of Unsubstituted Benzyl Ester (II.8): A: Reactions with H₂ as the Reductant: Unsubstituted porphyrin benzyl ester (II.7, 20 mg, 0.38 mmol, 1 equiv) was dissolved in the indicated solvent (3.8 mL) in a flame dried 10 mL round bottom flask. The flask was flushed with N₂ and the indicated catalyst was added (10 mol% was too small to measure, tip of a spatula was added which was likely more than the 10 mol%). A H₂ balloon was attached to the flask and the system was purged 3 xs with an aspirator. The reactions were stirred for 1 hour and the reaction mixture was filtered over a bed of celite. The solvent was removed under reduced pressure. In all cases, a single major product was observed by NMR of the crude. This product was determined as the partially hydrogenated porphyrin.

B: Reactions with 1,4-cyclohexadiene as the Reductant: Unsubstituted porphyrin benzyl ester (II.7, 20 mg, 0.38 mmol, 1 equiv) was dissolved in the indicated solvent (3.8 mL) in a flame dried 10 mL round bottom flask. The flask was flushed with N₂ and the indicated catalyst was added (10 mol% was too small to measure, tip of a spatula was added which was likely more than the 10 mol%). The reductant, 1,4-cyclohexadiene (47 μ L, 55 mg, 0.7 mmol, 1.8 equiv) was added. There was no reaction after 1 hour (by TLC). Then 1,4-cyclohexadiene (470 μ L, 550 mg, 7 mmol, 18 equiv) was added. After 24 hours, still no reaction by TLC. The mixture was filtered over celite to remove the catalyst and the solvent was removed under reduced pressure. The starting material was recovered as indicated by TLC and NMR.

(II.8): ¹H NMR (CDCl₃, 300 MHz): δ 10.34 (1H, s), 9.40 (2H, d, J = 4.5 Hz), 9.02 (2H, d, J = 4.5 Hz), 8.52 (2H, d, J = 8.7 Hz), 8.34 (2H, d, J = 8.4 Hz), 7.62 - 7.41 (5H, m), 7.28 (2H, s), 5.57 (2H, s), -3.17 (2H, br s).

Melting Point: decomposition 130 °C

Rf: 0.4 (100% CH₂Cl₂)

4-formyl phenyl benzoate (**II.9**): Terephthalaldehydic acid (450 mg, 3 mmol, 1 equiv), phenol (367 mg, 3.9 mmol, 1.3 equiv), EDC•HCl (748 mg, 3.9 mmol, 1.3 equiv), DMAP (476 mg, 3.9 mmol, 1.3 equiv) and dry dichloromethane (600 mL) were added to a flame dried 1 L round bottom flask while stirring under N₂ at room temperature. Stirring continued for 24 hours then the solvent was removed under reduced pressure. The crude product was purified by column chromatography conditions to provide the desired compound as an off-white solid (353 mg, 52%).

(**II.9**): ¹H NMR (CDCl₃, 300 MHz): δ 10.17 (1H, s), 8.38 (2H, d, *J* = 8.0 Hz), 8.04 (2H, d, *J* = 8.5 Hz), 7.45 (2H, m), 7.29 (1H, m), 7.22 (2H, m).

¹³C NMR (CDCl₃, 125 MHz): δ 191.5, 163.7, 150.6, 139.1, 134.2, 130.8, 129.5, 126.0, 121.7.

Mass Spectrum: [C₁₄H₁₁O₃]⁺ observed 227.0 m/z calculated 227.1 m/z

Melting Point: 94 - 96 °C

Rf: 0.2 (25% EtOAc/Hexanes)

Unsubstituted Porphyrin Phenyl Ester (**II.10**): To a 1 L, 3 neck flask equipped with stir bar and nitrogen adaptor 4-formyl phenyl benzoate (**II.9**, 339.3 mg, 1.5 mmol, 1 equiv), dipyrromethane (219.3 mg, 1.5 mmol, 1 equiv), 2-carboxypyrrole (285.3 mg, 3 mmol, 2 equiv), and dichloromethane (450 mL) were added at room temperature while stirring under N₂. The flask was shielded from light. After purging for 15 minutes, BF₃•OEt₂ (76.9 mg, 52 μL, 0.675 mmol,

0.45 equiv) was added. The mixture was stirred for 16 hours then *p*-chloranil (1.025 g, 4.17 mmol, 2.78 equiv) was added. After 1 hour, the solvent was removed under reduced pressure. The crude product was purified via column chromatography (30-70-100% dichloromethane/hexane) to provide the desired product as a red solid (25.1 mg, 3.2%).

(II.10): ^1H NMR (CDCl_3 , 300 MHz): δ 10.35 (1H, s), 10.28 (1H, s), 9.50 (4H, dd, $J = 4.5, 6.5$ Hz), 9.43 (2H, d, $J = 5.0$ Hz), 9.06 (2H, d, $J = 5.0$ Hz), 8.64 (2H, d, $J = 8.0$ Hz), 8.41 (2H, d, $J = 8.0$ Hz), 7.54 (2H, t, $J = 7.5$ Hz), 7.41 (2H, d, $J = 7.5$), 7.36 (1H, t, $J = 7.5$ Hz), -3.60 (2H, br. s).

Mass Spectrum: $[\text{C}_{33}\text{H}_{23}\text{N}_4\text{O}_2]^+$ observed 507.0 m/z calculated 507.2 m/z

Melting Point: decomposition 170 °C

Rf: 0.7 (100% CH_2Cl_2)

Zincated Unsubstituted Porphyrin Phenyl Ester (II.11): To a 10 mL round bottom flask, shielded from light, unsubstituted porphyrin phenyl ester (10 mg, 0.02 mmol, 1 equiv) was dissolved in CH_2Cl_2 (3 mL). Zinc acetate ($\text{Zn}(\text{OAc})_2$, large excess) was added. The reaction was stirred for 12 hours. The mixture was filtered through celite and purified by column chromatography (100% CH_2Cl_2) to provide the desired product as a pink solid (10 mg, 90%).

(II.11): ^1H NMR (CDCl_3 , 300 MHz): δ 10.25 (2H, s), 10.22 (1H, s), 9.45 (4H, s), 9.38 (2H, d, $J = 4.0$ Hz), 9.01 (2H, d, $J = 4.5$ Hz), 8.53 (2H, d, $J = 8.0$ Hz), 8.33 (2H, d, $J = 8.0$ Hz), 7.57-7.26 (5H, m)

Mass Spectrum: $[\text{C}_{33}\text{H}_{21}\text{N}_4\text{O}_2\text{Zn}]^+$ observed 569.0 calculated 569.1

Melting Point: decomposition 195 °C

Rf: 0.8 (100% CH_2Cl_2)

Zincated Unsubstituted Porphyrin Monolinker (**II.12**): To a 10 mL round bottom flask, shielded from light, unsubstituted porphyrin monolinker (10 mg, 0.02 mmol, 1 equiv) was dissolved in CH₂Cl₂ (3 mL). Zinc II acetate (Zn(OAc)₂, large excess) was added. The reaction was stirred for 12 hours. The mixture was filtered through celite and purified by column chromatography (100% CH₂Cl₂) to provide the desired product as a pink solid (11 mg, quantitative).

(**II.12**): ¹H NMR (CDCl₃, 300 MHz): δ 10.26 (2H, s), 10.18 (1H, s), 9.47-9.43 (6H, m), 9.08 (2H, d, *J* = 4.5 Hz), 8.44 (2H, d, *J* = 8.4 Hz), 8.34 (2H, d, *J* = 8.4 Hz), 4.48 (2H, t, *J* = 6.6 Hz), 3.53 (2H, t, *J* = 5.7 Hz), 2.01 (2H, quintet, *J* = 5.0, 14 Hz), 1.78 (2H, m), 1.72 (2H, m)

Mass Spectrum: [C₃₂H₂₇N₄O₃Zn]⁺ observed 579.1 calculated 579.1

Melting Point: decomposition 115 °C

R_f: 0.7 (10% EtOAc/CH₂Cl₂)

Unsubstituted Porphyrin Tweezer by Transesterification under basic conditions: For each reaction, three separate round bottom flasks were flame dried. In one flask, NaH (0.8 g, 20 mmol) was suspended in dry THF (20 mL). In the second round bottom, the monolinker (2 mg, 1 equiv) was dissolved in the indicated solvent (2 mL). To the monolinker, 2 mL of the NaH suspension or KHMDS (0.5 M in toluene, 0.12 mL, 60 μmol, 10 equiv) and HMPA (0.1 mL, 0.103 g, 0.5 mmol, 75 equiv) was added and the reaction mixture was stirred at room temperature for 30 minutes. In the third round bottom, the unsubstituted porphyrin phenyl ester (2 mg, 1 equiv) was dissolved in 2 mL of the indicated solvent. The phenyl ester solution was then added dropwise to the monolinker solution and the reaction was stirred for 12 hours. The reaction was quenched with HCl (aq, 2M, 1 mL). Then the organic was diluted with CH₂Cl₂ (5

mL), washed with water (5 mL, 3 xs) and dried with Na₂SO₄. The solvent was removed under reduced pressure. Crude NMR of the reaction mixtures indicated recovery of the starting materials.

5,5'-diformyl-2,2'-dipyrromethane (**II.14**): The unsubstituted, 2,2'-dipyrromethane (**II.1**, 0.7 g, 5 mmol, 1 equiv) was dissolved in dry DMF (5 mL, 4.72 g, 64 mmol, 12.8 equiv) in a flame dried 25 mL round bottom flask under N₂. The solution was chilled to 0 °C and benzoyl chloride (3 mL, 3.63 g, 26 mmol, 5 equiv) was added dropwise over 10 minutes. The reaction was stirred for 2 hours at 0 °C then warmed to room temperature. Reaction was stirred for another 2 hours at room temperature. The reaction was quenched with water (5 mL). The organic layer was diluted with EtOAc (5 mL), washed with water (10 mL, 2 xs) and dried with Na₂SO₄. The solvent was removed under reduced pressure and the crude residue was purified by column chromatography (50% EtOAc/Hexanes) to provide the desired product as black solid (195 mg, 20%).

(**II.14**): ¹H NMR (CDCl₃, 300 MHz): δ 9.84 (2H, br s), 9.36 (2H, s), 6.91 (2H, ab quartet, *J* = 2.4, 3.9 Hz), 6.13 (2H, m), 4.02 (2H, s)

¹³C NMR (CDCl₃, 125 MHz): δ 198.3, 132.2, 128.8, 129.1, 111.7, 42.1

Mass Spectrum: [C₁₁H₁₁N₂O₂]⁺ observed 203.1 calculated 203.1

Melting Point: 220 - 225 °C

R_f: 0.9 (50% EtOAc/Hexanes)

4-formyl-(5-hydroxypentyl)benzoate (**II.15**): 4-formylbenzoic acid (150 mg, 1 mmol, 1 equiv), 1,5-pentane diol (0.3 mL, 171.6 mg, 1.3 mmol, 1.3 equiv), EDC (249 mg, 1.3 mmol, 1.3 equiv) and DMAP (159 mg, 1.3 mmol, 1.3 mg) were dissolved in dry CH₂Cl₂ (200 mL). The mixture was stirred for 24 hours at room temperature under N₂. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (20-50-70% EtOAc/Hexanes). The desired product was isolated as a yellow oil (208 mg, 82%).

(**II.15**): ¹H NMR (CDCl₃, 500 MHz): δ 10.06 (1H, s), 8.15 (2H, d, *J* = 8.5 Hz), 7.91 (2H, d, *J* = 8.0 Hz), 4.34 (2H, t, *J* = 6.5 Hz), 3.66 (2H, t, *J* = 6.5 Hz), 2.92 (1H, br s), 1.80 (2H, m), 1.63 (2H, m), 1.52 (2H, m)

¹³C NMR (CDCl₃, 125 MHz): δ 191.9, 165.9, 139.4, 135.6, 130.4, 129.7, 65.8, 62.8, 32.5, 28.7, 22.6

Mass Spectrum: [C₁₃H₁₇O₄]⁺ observed 237.0 m/z calculated 237.1 m/z

R_f: 0.4 (50% EtOAc/Hexanes)

Pentane-1,5-diyl bis(4-formyl)benzoate (**II.16**): To dry CH₂Cl₂ (165 mL) in a 250 mL round bottom flask under N₂ was added, 4-formyl-(5-hydroxypentyl)benzoate (**II.15**, 170 mg, 0.82 mmol, 1 equiv), 4-formylbenzoic acid (160 mg, 1.1 mmol, 1.3 equiv), DMAP (131 mg, 1.1 mmol, 1.3 equiv) and EDC (205 mg, 1.1 mmol, 1.3 equiv). After 24 hours, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (100% CH₂Cl₂). The product was isolated as an off-white solid (204 mg, 68%)

(**II.16**): ¹H NMR (CDCl₃, 500 MHz): δ 10.06 (2H, s), 8.15 (4H, d, *J* = 8.0 Hz), 7.90 (4H, d, *J* = 7.0 Hz), 4.37 (4H, t, *J* = 7.0 Hz), 1.86 (4H, dt, *J* = 6.5, 7.5 Hz), 1.61 (2H, m)

^{13}C NMR (CDCl_3 , 125 MHz): δ 191.5, 165.5, 139.1, 135.2, 130.11, 129.5, 65.2, 28.3, 22.5

Mass Spectrum: $[\text{C}_{21}\text{H}_{21}\text{O}_6]^+$ observed 369.0 m/z calculated 369.13 m/z

Melting Point: 80 - 85 °C

Rf: 0.1 (100% CH_2Cl_2)

Pentane-1,5-diyl bis(4-(di(1H-pyrrol-2-yl)methyl)benzoate (**II.17**): Pentane-1,5-diyl bis(4-formyl) benzoate (**II.6**, 100 mg, 0.27 mmol, 1 equiv) was dissolved in pyrrole (0.44 mL, 455 mg, 6.8 mmol, 25 equiv) in a 50 mL round bottom flask under N_2 . Then trifluoroacetic acid (TFA, 2 μL , 2.5 μmol) was added. After 30 minutes, the reaction was diluted with 100 mL and the organic layer was washed with NaOH (aq, 0.1 M, 100 mL, 2 xs) and water (100 mL, 2 xs). The organic layer was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The excess pyrrole was removed by distillation and the residue was purified by column chromatography (80:20:1 EtOAc/Hexanes/ Et_3N) to provide the product as a brown solid (72 mg, 44%).

(**II.17**): ^1H NMR ($\text{CDCl}_3/\text{CD}_3\text{OD}$, 500 MHz): δ 7.81 (4H, d, J = 8.3 Hz), 7.15 (4H, d, J = 8.0 Hz), 6.59 (2H, m), 5.99 (2H, m), 5.71 (2H, m), 5.37 (2H, s), 4.21 (4H, t, J = 6.5 Hz), 1.74 (4H, m), 1.51 (4H, m)

^{13}C NMR ($\text{CDCl}_3/\text{CD}_3\text{OD}$, 125 MHz): δ 131.8, 129.5, 128.3, 117.2, 107.7, 106.9, 64.6, 43.8, 28.1, 22.4

Mass Spectrum: $[\text{C}_{37}\text{H}_{37}\text{N}_4\text{O}_4]^+$ observed 601.2 calculated 601.3

Melting Point: decomposition 215 °C

Rf: 0.23 (50% EtOAc/Hexanes)

Metalated Unsubstituted Porphyrin Tweezer (**II.18**): A: Zinc Templated Condensation: To a 5 mL round bottom flask, 5,5'-diformyl-2,2'-dipyrromethane (**II.14**, 50 mg, 0.24 mmol, 1 equiv) was dissolved in *n*-propylamine (1.5 mL). After 30 minutes, the excess amine was removed under reduced pressure. The crude product was dissolved in ethanol (12 mL) in a 25 mL round bottom flask, with pentane-1,5-diyl bis(4-(di(1H-pyrrol-2-yl)methyl)benzoate (**II.17**, 72 mg, 0.12 mmol, 0.5 equiv) and zinc II acetate (0.5 g, 2.4 mmol, 10 equiv). The reaction mixture was refluxed for 16 hours while exposed to air. The crude mixture was filtered through celite and the solvent was removed under reduced pressure. The desired product was not obtained by NMR.

B: Magnesium Templated Condensation: Pentane-1,5-diyl bis(4-(di(1H-pyrrol-2-yl)methyl)benzoate (**II.17**, 48 mg, 0.08 mmol, 1 equiv) and 5,5'-diformyl-2,2'-dipyrromethane (**II.14**, 32 mg, 0.16 mmol, 2 equiv) were dissolved in dry toluene (3 mL). The reaction mixture was heated to 80 °C then DBU (0.12 mL, 0.8 mmol, 10 equiv) and magnesium bromide (MgBr₂, 44 mg, 0.240 mmol, 3 equiv) were added. The reaction was refluxed for 19 hours while exposed to air. After cooling to room temperature, the mixture was filtered through celite and the solvent removed under reduced pressure. The desired product was not formed based on NMR.

5-(4-methylcarboxylphenyl)-10, 15, 20-tri(heptafluorobutryl)porphyrin (**II.19**): To a 3 L, three neck flask, shielded from light heptafluorobutrylaldehyde hydrate (0.94 g, 4.73 mmol, 1 equiv) and 2,2'-(2,2,3,3,4,4,4-heptafluorobutane-1,1-diyl)bis(1H-pyrrole) (C₃F₇ DPM, **II.21**, 3 g, 9.47 mmol, 2 equiv) were dissolved in dichloromethane (790 mL) while stirring at room temperature

under N₂. After 15 minutes, boron trifluoride diethyl etherate (0.05 mL, 62 mg, 0.44 mmol, 0.1 equiv) was added and the solution was stirred for 3 hours at room temperature. 4-Formyl methyl benzoate (0.77 g, 4.73 mmol, 1 equiv) was added and the reaction was stirred for an additional 16 hours, after which DDQ (1.1 g, 4.84 mmol, 1 equiv) was added. This was stirred for 24 hours. The reaction was then flushed through a silica pad with CH₂Cl₂ until the eluent changed from red to brown. The solvent was removed under reduced pressure and the reaction residue was dissolved in toluene (790 mL). To the solution DDQ (1.1 g, 4.84 mmol, 1 equiv) was added and the reaction was refluxed for 48 hours. The reaction was filtered through a silica pad with CH₂Cl₂ until the eluent changed from red to brown. The solvent was removed under reduced pressure to give the crude porphyrin. Purification by gradient column chromatography (100 Hexanes - 25% CH₂Cl₂/Hexanes) provided the desired porphyrin. Removal of solvent gave the porphyrin as a purple solid (660 mg, 15%). ¹H NMR matched literature reported spectrum.⁵³

(II.19): ¹H NMR (CDCl₃, 600 MHz): δ 9.57 (4H, br s), 9.38 (2H, br s), 8.80 (2H, d, *J* = 4.8 Hz), 8.45 (2H, d, *J* = 6.6 Hz), 8.18 (2H, br s), 4.13 (3H, s), -2.40 (2H, br s).

¹³C NMR (CDCl₃, 150 MHz): δ 166.9, 145.4, 144.9 (br), 133.7 (br), 133.3 (br), 131.7 (br), 130.6, 128.2, 123.4, 119.8 (m), 109.9 (m), 104.8 (m), 52.6

¹⁹F NMR (CDCl₃, 564 MHz): δ -77.21 (2F, br s), -79.16 (9F, m), -81.10 (4F, br s), -118.10 (2F, br s), -119.12 (4F, br s)

¹H/¹³C HMBC (CDCl₃, 600 MHz): δ 9.57/133.3, 9.38/131.7, 8.80/133.7, 8.45/128.0, 4.13/52.6

Mass Spectrum: [C₃₇H₁₈F₂₁N₄O₂]⁺ observed 949.2 m/z calculated 949.1 m/z

Melting Point: 226 - 232 °C

Rf: 0.8 (100% CH₂Cl₂)

5,15-di(4-methylcarboxylphenyl)-10, 20-tri(heptafluorobutryl)porphyrin (**II.20**):⁵³ To a 3 L, three neck flask heptafluorobutrylaldehyde hydrate (0.831 g, 3.85 mmol, 5 equiv) and pyrrole (0.22 mL, 0.207 g, 3.09 mmol, 4 equiv) were dissolved in dichloromethane (460 mL) while stirring at room temperature under N₂. After 15 minutes, boron trifluoride diethyl etherate (0.07 mL, 0.087 g, 0.616 mmol, 0.8 equiv) was added and the solution stirred for 4 hours at room temperature under N₂. Next, terephthalaldehydic acid methyl ester (0.126 g, 0.77 mmol, 1 equiv) was added and stirring continued for 2 hours. Then *p*-chloranil (1.13 g, 4.6 mmol, 8 equiv) was added and the solution was stirred for an additional 2 hours at room temperature under N₂. The solvent was removed under reduced pressure to give the crude product, which was purified via column chromatography (10% EtOAc/CH₂Cl₂). The desired product was obtained as a purple solid (85 mg, 12%)

(**II.20**): ¹H NMR (CDCl₃, 500 MHz): δ 9.56 (4H, s), 9.37 (2H, s), 8.80 (2H, d, *J* = 5.0 Hz), 8.45 (2H, d, *J* = 7.5 Hz), 4.12 (3H, s), -2.40 (2H, s)

Melting Point: 210 - 214 °C.

Rf: 0.8 (10% EtOAc/CH₂Cl₂)

2,2'-(2,2,3,3,4,4,4-heptafluorobutane-1,1-diyl)bis(1*H*-pyrrole) (**II.21**): HCl Catalyzed⁵³

Heptafluorobutrylaldehyde hydrate (0.5 g, 2.52 mmol, 1 equiv) and pyrrole (0.35 mL, 5 mmol, 2 equiv) were dissolved in THF (10 mL) in a 50 mL round bottom flask while stirring under N₂ at room temperature. After 15 minutes HCl was added and the mixture was refluxed for 2 hours.

Note: When 0.2 mL HCl (conc) was used, **II.21a** was the major product, but when 2 mL HCl (conc) was used, **II.21** was the major product. The reaction mixture was neutralized with NaHCO₃ (aq sat, 15 mL) and diluted with dichloromethane (10 mL). The organic layer was washed with NaHCO₃ (aq sat, 20 mL, 2 xs), H₂O (20 mL, 1 xs) and then dried with Na₂SO₄. The solvent was removed under reduced pressure to give the crude product. This was purified via column chromatography to give the desired product as a brown semi-solid.

(II.21): ¹H NMR (CDCl₃, 600 MHz): δ 8.11 (2H, br s), 6.75 (2H, m), 6.22 (2H, br s), 6.18 (2H, m), 4.92 (1H, t, *J* = 17.0 Hz)

¹³C NMR (CDCl₃, 150 MHz): δ 122.1, 118.8, 116.4 (m), 109.48, 109.36 (m), 109.22(m), 108.9, 40.7 (t, *J* = 18.75 Hz)

¹⁹F NMR (CDCl₃, 564 MHz): δ -80.64 (3H, quintet, *J* = 11.0, 22.3 Hz), -113.08 (2H, m), -124.94 (2H, m)

¹⁹F / ¹³C HMQC (CDCl₃, 564 MHz): δ -80.7/109.36, -113.1/109.22, -124.9/116.4

Mass Spectrum: [C₁₂H₁₀F₇N₂]⁺ observed 314.9 m/z calculated 315.1 m/z

Melting Point: 40 - 42 °C

R_f: 0.5 (100% CH₂Cl₂)

(II.21a): ¹H NMR (CDCl₃, 300 MHz): δ 8.24 (1H, br s), 6.82 (1H, m), 6.31 (1H, m), 6.18 (1H, m), 5.22 (1H, d, *J* = 4.0 Hz), 2.41 (1H, s).

TFA and InCl₃ Catalyzed Reactions: Pyrrole (6.9 mL, 6.7 g, 100 mmol, 100 equiv) and heptafluorobutrylaldehyde hydrate (314 mg, 1 mmol, 1 equiv) were added to a 100 mL round bottom flask under N₂ at room temperature. Then the catalyst InCl₃ (22.1 mg, 0.1 mmol, 0.1

equiv) or trifluoroacetic acid (7.6 μ L, 11.4 mg, 0.1 mmol, 0.1 equiv) was added and the reaction was stirred for 4 hours. The reaction was quenched with NaOH (aq, 2M, 0.5 mL) and diluted with CH₂Cl₂ (20 mL). The organic layer was washed with NaHCO₃ (aq sat, 20 mL, 2 xs) and water (20 mL, 1 xs) then dried with Na₂SO₄. The solvent was removed under reduced pressure. The desired product was not observed by crude NMR due to the excess of pyrrole. The crude was subjected to gradient column chromatography (10 - 100% EtOAc/Hexanes). The desired product was not isolated.

5-(4-carboxyphenyl)-10,15,20-tris(heptafluoropropyl) porphyrin - C₃F₇ Acid (**II.22**):⁵³

C₃F₇ methyl ester (**II.19**, 530mg, 0.56 mol, 1 equiv) was dissolved in HCl (conc, 265mL) and trifluoroacetic acid (TFA, conc, 135 mL). The reaction mixture was heated to 60 °C for 12 hours. The reaction mixture was diluted with CH₂Cl₂ then neutralized by slow addition of NaHCO₃ (solid). When neutralized, water was added to dissolve the excess NaHCO₃. The water layer was removed then the organic layer was washed with water (3xs) and dried with Na₂SO₄. The solvent was removed under reduced pressure and the crude porphyrin was purified by column chromatography (10% MeOH/CH₂Cl₂) to yield the desired product as a purple solid (**II.22**, 341 mg, 65%). Carbon and proton NMR indicate impurities in the alkyl region of the spectrum. The product was taken to the next step without further purification.

(**II.22**): ¹H NMR (CDCl₃/CD₃OD, 600 MHz): δ 9.37 (4H, br s), 9.18 (2H, m), 8.64 (2H, t, J = 4.8 Hz), 8.29 (2H, t, J = 6.6 Hz), 8.02 (2H, br s).

¹³C NMR (CDCl₃ /CD₃OD, 150 MHz): δ 168.2, 144.9, 133.8, 133 (br), 131 (br), 130.7, 128.1, 123.3, 119 (m), 109.7 (m), 104.3 (m), 109.22(m), 108.9, 40.7 (t, J = 18.75 Hz)

^{19}F NMR (CDCl_3 / CD_3OD , 470 MHz): δ -78.8 (2F, br s), -80.8 (9F, m), -82.6 (4F, br s), -119.6 (2F, br s), -120.6 (4F, br s)

Mass Spectrum: $[\text{C}_{36}\text{H}_{16}\text{F}_{21}\text{N}_4\text{O}_2]^+$ observed 935.2 m/z calculated 935.1 m/z

Melting Point: 170 - 175 °C

Rf: 0.2 (10% MeOH/ CH_2Cl_2)

C₃F₇ Monolinker (II.23): C₃F₇ Acid (**II.22**, 25 mg, 0.026 mmol, 1 equiv), 1,5-pentane diol (3.7 μL , 3.65 mg, 0.035 mmol, 1.3 equiv), EDC (6.7 mg, 0.035 mmol, 1.3 equiv) and DMAP (4.27 mg, 0.035 mmol, 1.3 equiv) were dissolved in CH_2Cl_2 (10 mL) in a 20 mL vial. The reaction was shielded from light and stirred for 4 hours then the solvent was removed under reduced pressure. The crude was purified by column chromatography (25% EtOAc/ CH_2Cl_2) to yield the desired product as a purple solid (20 mg, 75%).

(II.23): ^1H NMR (CDCl_3 , 600 MHz): δ 9.56 (4H, br s), 9.37 (2H, m), 8.06 (2H, t, J = 4.8 Hz), 8.45 (2H, t, J = 6.6 Hz), 8.20 (2H, br s), 4.54 (2H, t, J = 6.6 Hz), 3.76 (2H, t, J = 6.0 Hz), 1.97 (2H, quintet, J = 7.2 Hz), 1.78-1.65 (4H, m), -2.40 (2H, br s)

^{13}C NMR (CDCl_3 , 150 MHz): δ 166.4, 145.3, 144.9 (br), 134.1, 133.7 (br), 133.5 (br), 131.6 (br), 130.8, 128.1, 123.3, 119.6 (m), 109.7 (m), 104.8 (m), 65.4, 62.8, 32.4, 28.7, 22.5

^{19}F NMR (CDCl_3 , 470 MHz): δ -79.4 (2F, br s), -81.3 (9F, m), -83.2 (4F, br s), -120.5 (2F, br s), -121.2 (4F, br s)

Mass Spectrum: $[\text{C}_{41}\text{H}_{26}\text{F}_{21}\text{N}_4\text{O}_3]^+$ observed 1021.2 m/z calculated 1021.2 m/z

Melting Point: 244 - 247 °C

Rf: 0.7 (10% EtOAc/ CH_2Cl_2)

C₃F₇ Free Tweezer (**II.24**): To a 20 vial, C₃F₇ Monolinker (**II.23**, 15 mg, 0.015 mmol, 1 equiv), C₃F₇ Acid (**II.22**, 18 mg, 0.02 mmol, 1.3 equiv), DMAP (2.4 mg, 0.02 mmol, 1.3 equiv), EDC (3.8 mg, 0.02 mmol, 1.3 equiv) and CH₂Cl₂ (10 mL) were added. The vial was shielded from light and the reaction was stirred for 12 hours at which point the solvent was removed under reduced pressure. The crude tweezer was purified by column chromatography (100% CH₂Cl₂) to obtain the desired product as a purple solid (22 mg, 76%).

(**II.24**): ¹H NMR (CDCl₃, 600 MHz): δ 9.46 (4H, br s), 9.38 (4H, br s), 9.14 (4H, br s), 8.72 (4H, t, *J* = 5.5 Hz), 8.52 (4H, t, *J* = 7.5 Hz), 8.20 (4H, br s), 4.68 (4H, t, *J* = 6.5 Hz), 2.15 (4H, quintet, *J* = 7.5 Hz), 1.96 (2H, m), -2.67 (4H, br s)

¹³C NMR (CDCl₃, 125 MHz): δ 166.5, 145.4, 144.8 (br), 138.9 (br), 136.8 (br), 134.2, 133.4-133.0 (br), 131.2 (br), 130.7, 128.1, 123.2, 119.4 (m), 109.8 (m), 104.5 (m), 65.2, 28.6, 22.9

¹⁹F NMR (CDCl₃, 470 MHz): δ -79.3 (4F, br s), -81.35 (6F, t, *J* = 9.9 Hz), -81.42 (12F, t, *J* = 9.9 Hz), -83.7 (8F, br s), -120.3 (4F, br s), -121.5 (8F, br s)

Mass Spectrum: [C₇₇H₃₈F₄₂N₈O₄]⁺ observed 1937.3 calculated 1937.2

Melting Point: 203 - 207 °C

R_f: 0.85 (100% CH₂Cl₂)

C₃F₇ Zincated Tweezer (**II.25**): To a 20 vial, C₃F₇ Free Tweezer (**II.24**, 10 mg, 0.005 mmol, 1 equiv), zinc II acetate (excess) and CH₂Cl₂ (5 mL) were added. The vial was shielded from light and the reaction was stirred for 4 hours at which point the solvent was removed under reduced pressure. The crude tweezer was purified by column chromatography (100% CH₂Cl₂) to obtain the desired product as a purple solid (10 mg, 96%).

(II.25): ^1H NMR (d_6 -Acetone, 600 MHz): δ 9.63 (4H, br s), 9.61 (4H, br s), 9.36 (4H, br s), 8.93 (4H, d, $J = 4.8$ Hz), 8.52 (4H, t, $J = 7.2$ Hz), 8.34 (4H, br s), 4.64 (4H, t, $J = 6.5$ Hz), 2.15 (4H, quintet, $J = 7.8$ Hz), 1.97 (2H, t, $J = 7.8$ Hz).

^{13}C NMR (d_6 -Acetone, 125 MHz): δ 166.9, 150.1 (br), 149.8 (br), 149.5 (br), 148.7 (br), 147.3 (br), 135.2, 134.9 (br), 134.2 (br), 133.2 (br), 131.4, 128.6, 125.3, 122-118 (m), 112-108 (m), 105.9 (t, $J = 12.5$ Hz), 103.2 (t, $J = 12.5$ Hz), 65.8, 30.6, 23.6.

^{19}F NMR (d_6 -Acetone, 470 MHz): δ -79.2 (4F, br s), -77.9 (8F, br s), -80.02 (6H, t, $J = 9.9$ Hz), -80.12 (12F, t, $J = 9.9$ Hz), -118.7 (4F, br s), -119.2 (8F, br s).

gHSQC (d_6 -Acetone, 600 MHz): (9.63, 134.2), (9.61, 134.6), (9.36, 133.2), (8.93, 134.9), (8.52, 128.6), (4.64, 65.8), (2.05, 30.6), (1.97, 23.6).

gCOSY (d_6 -Acetone, 600 MHz): (9.36, 8.93), (4.64, 2.15), (2.15, 1.97).

gHMBC (d_6 -Acetone, 600 MHz): (9.63, 150.1), (9.63, 134.9), (9.61, 148.7), (9.61, 134.2), (9.36, 149.5), (9.36, 134.9), (8.93, 149.8), (8.93, 133.2), (8.52, 147.3), (4.64, 166.9), (4.64, 30.6), (4.64, 23.6), (2.15, 65.8), (2.15, 30.6), (2.15, 23.6), (1.97, 65.8), (1.97, 30.6).

Mass Spectrum: $[\text{C}_{77}\text{H}_{34}\text{F}_{42}\text{N}_8\text{O}_4\text{Zn}_2]^+$ observed 2061.1 calculated 2061.1

Melting Point: 225 - 228 $^{\circ}\text{C}$

R_f: 0.8 (100% CH_2Cl_2)

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Chapter III

The Effects of Porphyrin Tweezer Linker Lengths on ECCD

Signals with 1,n-Glycols

III.1: Background of the Zn-TPFP-Tweezer

First reported in 2007 by our lab, the Zn-TPFP-Tweezer was designed and employed for the ECCD analysis of chiral diols and epoxy alcohols.^{1,2} This tweezer was designed because, the Zn-TPP-Tweezer was found inefficient for the evaluation of hydroxyl containing chiral molecules without first derivatizing the hydroxyl to a nitrogen containing functionality.³⁻⁶ Derivatization requires milligram quantities of substrate for the chemical transformation. However, if ECCD analysis could be conducted on the chiral diol, without first derivatizing, only micrograms of the substrate is required. This is beneficial in cases where limited amounts of the substrate are available. Therefore, Dr. Xiaoyong Li undertook the task of developing and synthesizing a tweezer that was capable of binding to hydroxyl functionalities. An electron deficient porphyrin tweezers was envisioned. The electron deficiency was hypothesized to withdraw electron density from the zinc center of the porphyrin and thereby increase the Lewis acidity of the metal. With the increased Lewis acidity, oxygen containing functionalities would have stronger binding interactions with the metal and stable ECCD active complex might form. Thus, ECCD analysis of chiral molecules with oxygen containing functional groups might be achieved without derivatizing the molecule.

A series of porphyrin tweezers with increasing electron deficiency was synthesized.⁷ Ultimately, the most electron deficient tweezer, Zn-TPFP-Tweezer was found most reliable. The

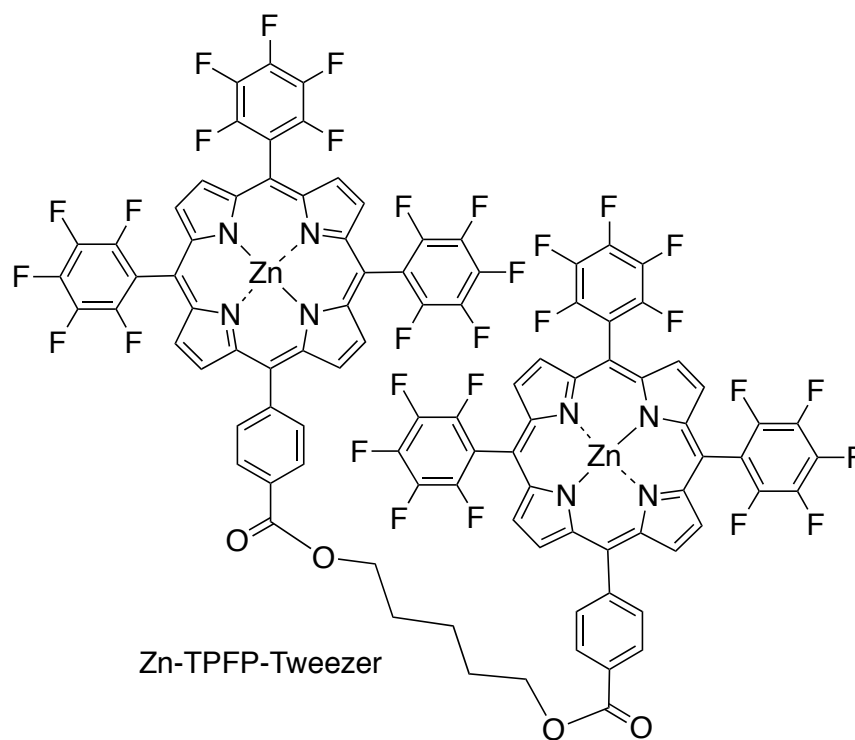


Figure III.1: Structure of the Zn-TPFP-Tweezer.⁸

Zn-TPFP-Tweezer, features two zincated 10,15,20-tris(pentafluorophenyl)-5-benzoate porphyrins joined by a 1,5-pentane diol linker (Figure III.1). When compared to Zn-TPP-Tweezer, the binding of hydroxyl functionalities, such as isopropanol, is about 100 fold larger with Zn-TPFP-Methyl Ester as compared to Zn-TPP-Methyl Ester.⁸ The binding event is essentially the donation of the oxygen lone pair electrons into the lowest unoccupied molecular orbital (LUMO) of the zinc. The energies of the zinc centers of Zn-TPFP-Methyl Ester as compared to Zn-TPP-Methyl Ester were calculated and the E_{LUMO} for Zn-TPFP-Methyl Ester was found to be lower than the E_{LUMO} of the Zn-TPP-Methyl Ester. This means E_{LUMO} of Zn-TPFP-Methyl Ester is closer in energy to the lone pair electrons of the oxygen, therefore, there is greater overlap of the orbitals, greater sharing of the electrons and tighter binding of the substrate as demonstrated by the larger K_a (association constant) values. These calculations

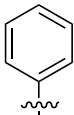
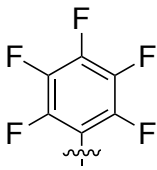
	Zn-TPP	Zn-TPFP
Meso substituent =		
E_{LUMO} (eV) =	3.93	2.57
K_a <i>i</i> PrOH (M^{-1}) =	49	2,170

Figure III.2: Comparison of E_{LUMO} and K_a values for Zn-TPP-Methyl Ester and Zn-TPFP-Methyl Ester. The lower E_{LUMO} of Zn-TPFP-Methyl Ester is the reason for the larger K_a with isopropanol (*i*PrOH).⁸

support the hypothesis that an electron deficient porphyrin will withdraw electron density from the zinc causing the zinc to become a stronger Lewis acid. As said, this tweezer was then employed in the evaluation of vicinal chiral diols and epoxy alcohols.^{2,8}

Traditionally, the absolute configuration of vicinal diols has been assigned by NMR derivatization techniques such as Mosher ester,⁹⁻¹⁵ chemical transformation to a known molecule or non-tweezer based ECCD methods. The ECCD methodologies require derivatization to the dibenzoate,¹⁶⁻²⁰ a metal complex²¹⁻²⁶ or cyclic derivative²⁷⁻²⁹ prior to analysis. Vicinal diols had presented a particular challenge in that, the benzoate methodology would fail for *erythro* vicinal diols (Figure III.3).^{17,18,20} The most energetically favorable conformation of these diols places the hydroxyl groups, and the resulting benzoate, functionalities *anti* to one another. Being at a 180° displacement, no ECCD signal would be observed. The most energetically favorable conformation of the *threo* diols placed the hydroxyl groups gauche to one another and at an angle of 60° , an ECCD signal would be observed with the dibenzoate methodology.

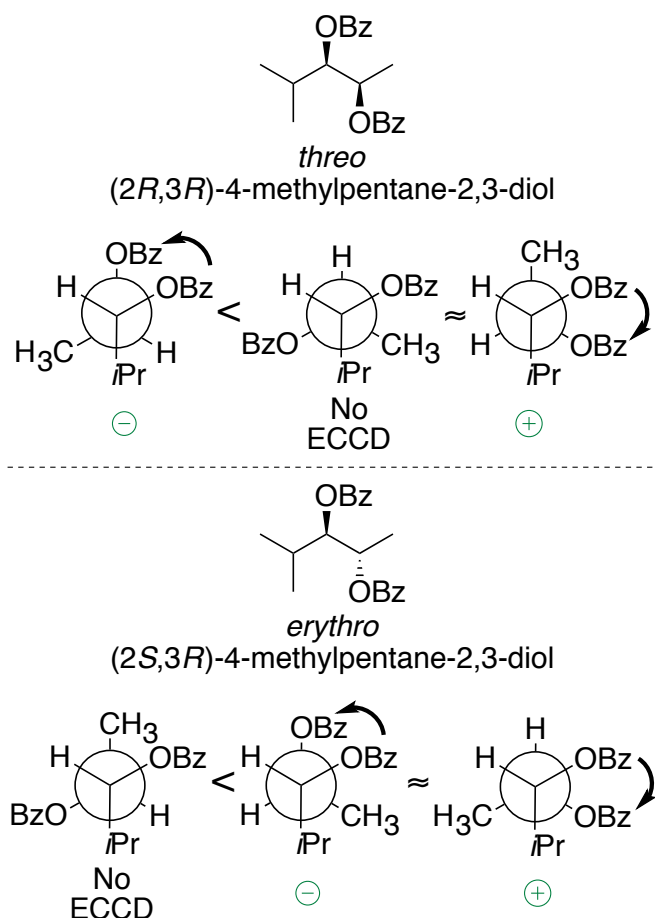


Figure III.3: ECCD/Dibenzoate methodology for vicinal diols. The Newman projections of the derivatized diols are shown. The most energetically favorable conformation of the *threo* diol is expected to give a negative ECCD signal whereas the *erythro* diol would show no ECCD due to the *anti* configuration of the chromophores.^{17,18,20}

Analysis of vicinal diols with the Zn-TPFP-Tweezer was conducted and was found to provide consistent and reliable ECCD signals for both the *threo* and *erythro* diols thus providing an ECCD methodology for the assignment of configuration of *erythro* diols.⁸ Additionally, ECCD with the tweezer did not require derivatization of the diol. The ECCD data obtained from this study was used to develop a mnemonic for the assignment of configuration of vicinal diols (Figure III.4). For both the *threo* and *erythro* diols, the diol is thought to be oriented such that

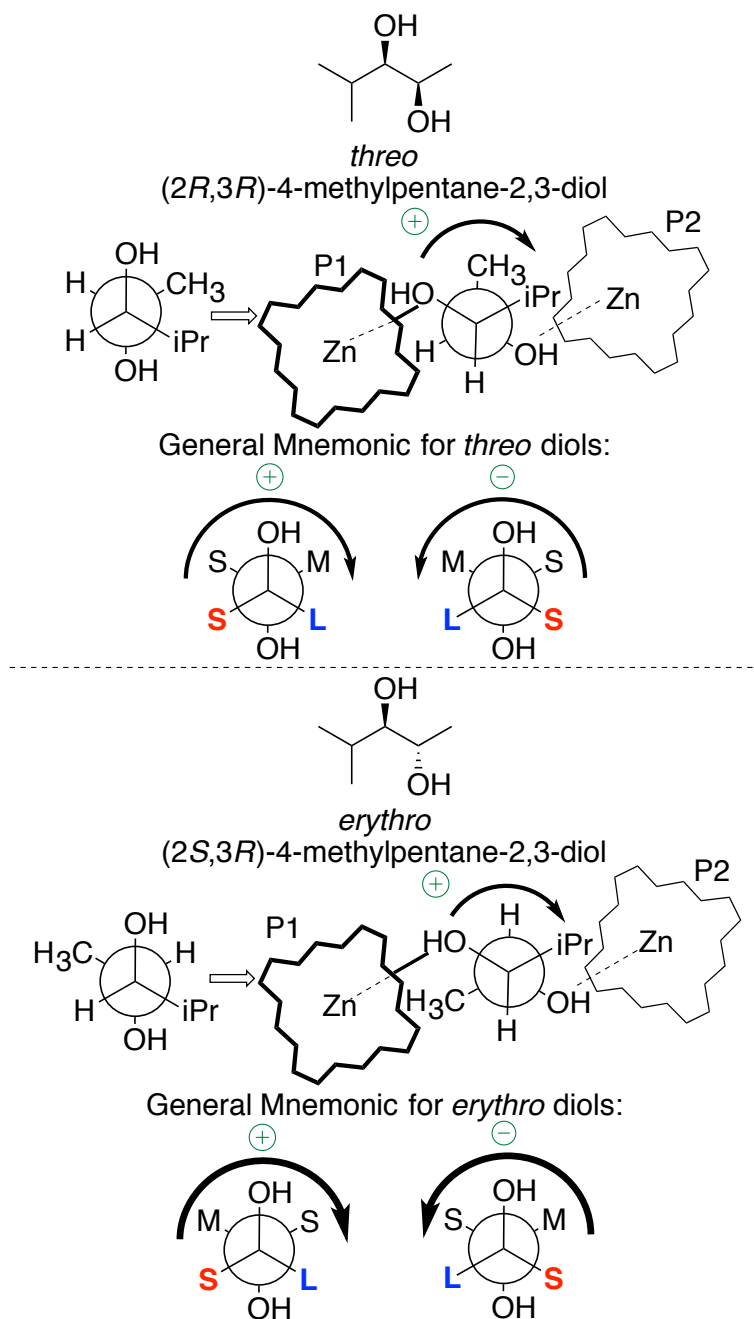


Figure III.4: The mnemonic for ECCD analysis of vicinal diols with Zn-TPFP-Tweezer. A specific example is given for each case. Newman projection is likely the conformation of the diol when bound to the tweezer. P1 rotates away from the large group and P2 rotates away from P1 to generate a helicity specific to the configuration of the diol. The bold arrows indicate the relative orientation of the porphyrins.

the hydroxyl groups are *anti* to one another to minimize interactions between the porphyrins. The discrimination occurs at the center bearing the largest group. For the diols shown in Figure III.4, the isopropyl group is the largest group. The porphyrin, P1, will move away from this large isopropyl toward the smaller hydrogen. The back porphyrin, P2, will then move the opposite direction of P1 to again minimize porphyrin-porphyrin interactions. Therefore, for the *threo* diols, any diol bearing the same configuration as (2*R*,3*R*)-4-methylpentane-2,3-diol would be expected to give a positive ECCD signal. Enantiomeric or pseudoenantiomeric diols are expected to generate a negative ECCD.

As for the *erythro* diols, a diol sharing the configuration of (2*S*,3*R*)-4-methylpentane-2,3-diol should give a positive ECCD.⁸ Again a pseudoenantiomeric diol should generate a negative ECCD signal. The orientation of P1 to P2 is indicated by the bold arrow and the predicted sign is shown by the plus or minus sign. In total, 11 *erythro* and 14 *threo* substrates (diols, amino alcohols and diamines) were tested. In all cases, the sign of the observed ECCD signal matched the sign predicted by the mnemonic. The success of the tweezer based methodology lies in the means of chiral discrimination. The working mnemonic considers each chiral center independently and the center bearing the largest substituent drives the transfer of chirality to the tweezer.

III.2: ECCD Study of Chiral 1,*n*-Glycols Using the Original Zn-TPFP-Tweezer

Methodologies for the configuration for 1,*n*-glycols have been reported with limited success therefore, a general and reliable method for assigning absolute stereochemistry is desired. 1,*n*-glycols are encountered in the natural product arena including biologically active

molecules. Families of natural products such as calyculins,^{30,31} fumonisins,³²⁻³⁵ swinholides,³⁶⁻³⁹ amphidinols⁴⁰⁻⁴⁴ and prymnesins^{45,46} contain poly hydroxylated acyclic carbon chains. Assignment of the correct stereochemistry of highly hydroxylated compounds is crucial as activity and function of bioactive molecules can be affected by changes in stereochemistry.^{47,48} Thus far, the most successful means of establishing stereochemistry has been through x-ray crystallography,³⁹ chemical correlation^{32,33,37,38,49,50} or total synthesis via stereoselective transformations.^{35,43,44,51} NMR methodologies are known and are typically only successful for 1,2- (vicinal) or 1,3-diols.^{14,15,52,53} Glycols where the hydroxyls are separated by a large number carbons are typically highly flexible, except when a part of a rigid cyclic system. The highly flexible nature means that the molecule can adopt a number of low energy conformations that complicate NMR analysis.

ECCD analysis of configuration, like NMR, has seen limited success with 1,2- and 1,3-diols and chemical transformation to a dibenzoate or cyclic derivative.^{28,29,54,55} One such example of a cyclic ECCD system for vicinal, 1,3- and 1,4-diols was described by Superchi and coworkers in 2010 (Figure III.5).²⁸ This methodology requires the derivatization of the diol of interest as a biphenyl dioxolane. The equilibrium between the *P* and *M* biphenyl dioxolanes is disrupted by the chiral centers of the diol to favor the helicity with the least steric repulsion. The ECCD of the helical biphenyl unit can then be recorded and the sign of the signal can be correlated to the configuration of the diol. They found that acyclic diols bearing an (*R*) or *anti* (*R,R*) configuration and cyclic diols with a *syn* (*S,R*) configuration favored the *M* helicity of the biphenyl and a negative ECCD was observed. The *P* helicity would be favored for diols of the opposite configurations and a positive sign would be expected. The authors examine five diols

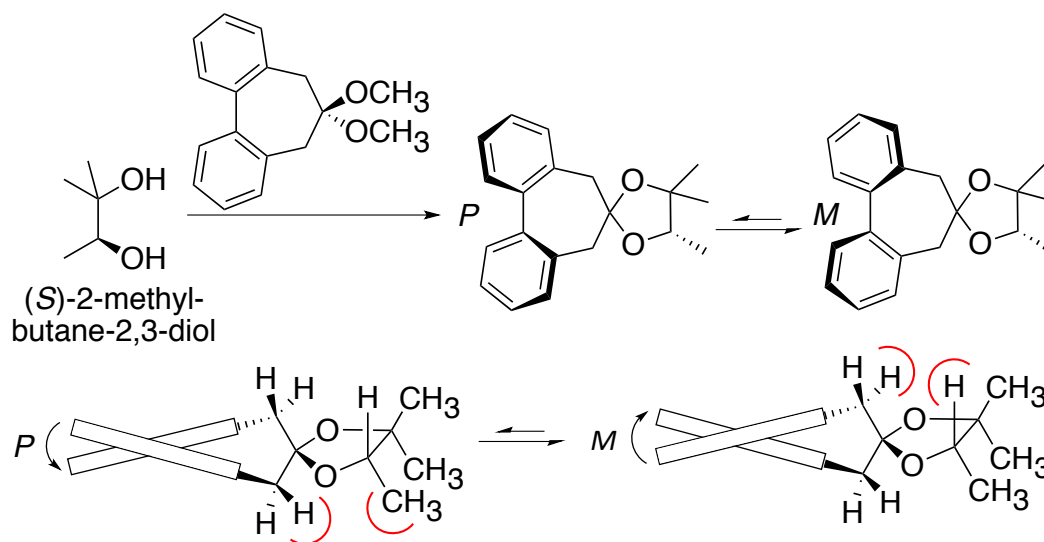


Figure III.5: Superchi and coworkers biphenyl dioxolane system for ECCD of diols. The equilibrium between the *P* and *M* biphenyl dioxolanes favors the conformation with the least steric interaction. For (*S*)-2-methylbutane-2,3-diol the equilibrium favors *M* and a negative ECCD signal is observed.²⁸

with this methodology and found the observed ECCD signals match the sign predicted by their mnemonic. However, the stereochemistry of the diol was problematic. For acyclic systems, an *anti* configuration gave the best results and the *syn* cyclic diols worked well however, *syn* acyclic and *anti* cyclic diols would not generate ECCD. Also, the methodology could not be extended to include diols separated by more than four carbons.

A methodology reported in 2004 by Molinski and coworkers, described the determination of stereochemistry for 1,*n*-glycol (*n* = 5, 7, 9).^{56,57} The diols were first derivatized as the porphyrin benzoates, then incorporated into a liposome. The liposome serves to rigidify the flexible diol backbone and allow for efficient exciton coupling of the porphyrins across long distance. Without the liposome, the derivatized diol is free to adopt any number of conformations and as a result ECCD is not observed. After optimization of the lipid

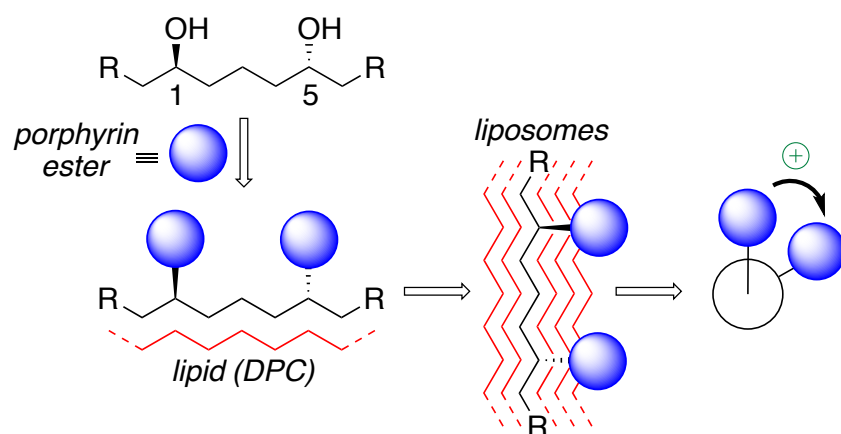


Figure III.6: ECCD protocol for 1,*n*-glycols (*n* = 5, 7, 9) described by Molinski and coworkers. The diol is first derivatized by a porphyrin benzyl ester then the derivatized diol is incorporated in a liposome of distearoyl-*sn*-glycero-3-phosphatidylcholine (DPC). Diols of (*R,R*) configuration gave a positive ECCD signal.^{56,57}

length, ECCD of a variety of 1,*n*-glycols (*n* = 5, 7, 9) were recorded. The authors determined that diols bearing an (*R,R*) configuration gave a positive ECCD signal and (*S,S*) diols generated a negative signal. *Meso* 1,5- and 1,9- diols were subjected to the ECCD conditions but only baseline signal was observed. Also, 1,7- and 1,9- diols gave the most intense signals whereas 1,5-diols produced moderate ECCD but diols of other lengths were not examined. Therefore, a general ECCD protocol for 1,*n*-glycols was still unknown.

Although progress had been made toward efficient means of determining the absolute configuration of 1,*n*-glycols, a general and robust methodology was still desired. Following the completion of the vicinal diol study, Dr. Li envisioned extending the Zn-TPFP-Tweezer ECCD methodology to include 1,*n*-glycols. The glycols were synthesized by epoxidation of the corresponding diene followed by Jacobsen's HKR to provide the chiral epoxides.⁵⁸⁻⁶⁰ These epoxides were subjected to LAH ring opening to generate the chiral glycols. These glycols were

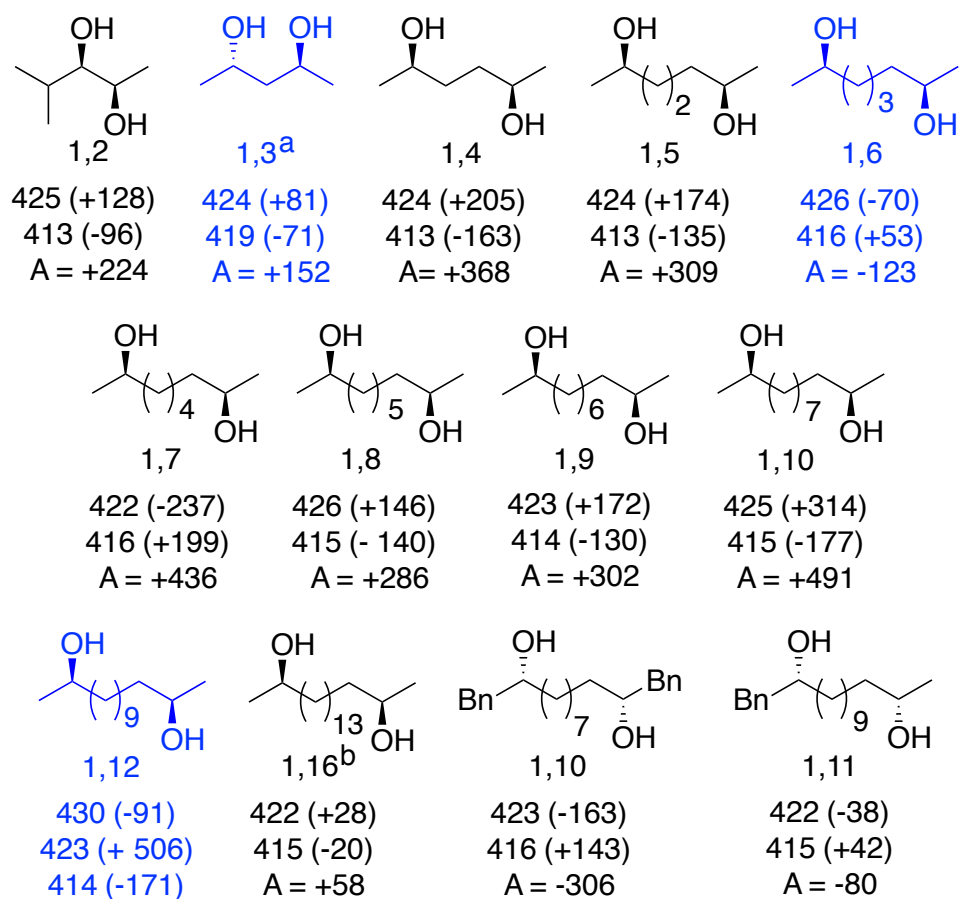


Figure III.7: The ECCD results for the 1,*n*-glycols with C5-Zn-TPFP-Tweezer. The glycols highlighted in blue generated ECCD responses that did not match the general trend for the series. All measurements: 0 °C, hexanes, 40 equivalents glycol. a: 100 equivalents glycol. b: 5 °C, 100 equivalents glycol, 5% CH₂Cl₂/hexanes.⁶¹

then submitted to ECCD analysis with Zn-TPFP-Tweezer (C5-Zn-TPFP-Tweezer), the results of which are summarized in Figure III.7. Of the twelve (*R,R*) glycols, ten provided an ECCD signal with a positive sign.⁶¹ It was reasoned that the (*R,R*) configuration induces a clockwise helicity into the porphyrin tweezer therefore, all of the (*R,R*) substrates should generate a positive ECCD and the (*S,S*) substrate should provide a negative ECCD signal. There were however three results that did not fit with the general trend. First, (2*S*,4*S*)-pentane-2,4-diol (1,3-diol) was

expected to give a negative signal and (2*R*,7*R*)-octane-2,7-diol (1,6 diol) should have produced a positive sign however, both glycols generated ECCD signals of the opposite sign. Also, (2*R*,13*R*)-tetradecane-2,13-diol (1,12-diol) provided a complex trisignate ECCD curve.

These results indicated that re-engineering of the tweezer was required. The porphyrin had been optimized to enhance the Lewis acidity of the zinc and promote binding of oxygen functionalities therefore, the porphyrin unit was to remain as the tris(pentafluorophenyl) porphyrin. Therefore, other variables of the porphyrin tweezer had to be considered. A study conducted Dr. Marina Tanasova showed that shortening the linker between the porphyrin units enhanced ECCD signals for evaluation of chiral diamines and carboxylic acids with Zn-TPP-Tweezer.⁶ By changing the linker from a five methylene unit (C5-Zn-TPP-Tweezer) to a three methylene unit (C3-Zn-TPP-Tweezer), the ECCD signals were stronger for most of the substrates evaluated. Selected results with chiral diamines are summarized in Figure III.8. It was reasoned

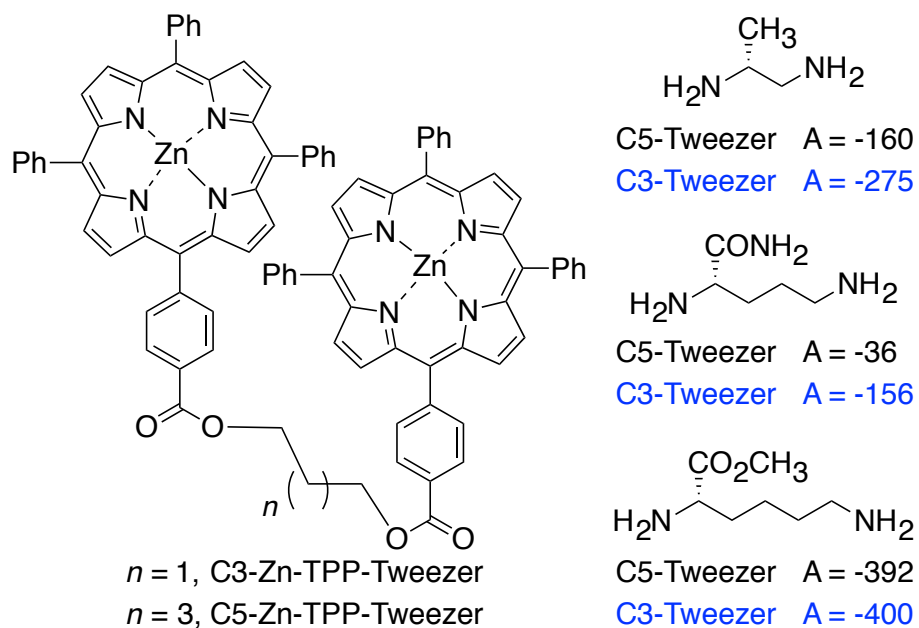


Figure III.8: Summary of ECCD results of the Zn-TPP-Tweezers and diamines. In general, the amplitudes are larger with the C3-Zn-TPP-Tweezer due to the shorter linker.⁷⁸

that by shortening the linker length, the tweezer had fewer degrees of freedom. Furthermore, the binding pocket between the two porphyrins is smaller for the tweezer with the shorter linker. Therefore, the substrate-tweezer complex with the C3-Zn-TPP-Tweezer would have fewer degrees of freedom, should be more rigid due to the smaller binding pocket and would favor a single ECCD active conformation. This would then lead to more robust ECCD signals. With the results of this study in mind, a series of Zn-TPFP-Tweezers were envisioned to vary the size of the binding pocket of the tweezer.

III.3: Design and Synthesis of Zn-TPFP-Tweezers with Varied Linker Lengths

The drive for changing the linker length was initiated by the proposed mode of binding for a given substrate with a porphyrin tweezer. It was hypothesized that there were two ways in which the glycol could fit in the binding pocket of Zn-TPFP-Tweezer (C5-Zn-TPFP-Tweezer), either the porphyrins are forced apart (Figure III.9 A) or the glycol folds into a high energy conformation to fit in the pocket (Figure III.9 B). First, binding of the substrate could force the porphyrins apart. The porphyrins are thought to be co-facial when the substrate is bound. As the glycol becomes longer, the porphyrins would be pushed farther apart such that the porphyrins remain co-facial but the angle and distance between them increases. It is believed that at some point the linker between the porphyrins is too short and the porphyrins can not separate enough to accommodate the length of the glycol. Alternatively, if the porphyrins are not separating, the glycol could fold to fit the binding pocket defined by the tweezer. However, the glycol would wrap into a high energy, non-linear, conformation to bind to the tweezer. The unfavorable conformation of either the tweezer or the glycol would result in the unreliable

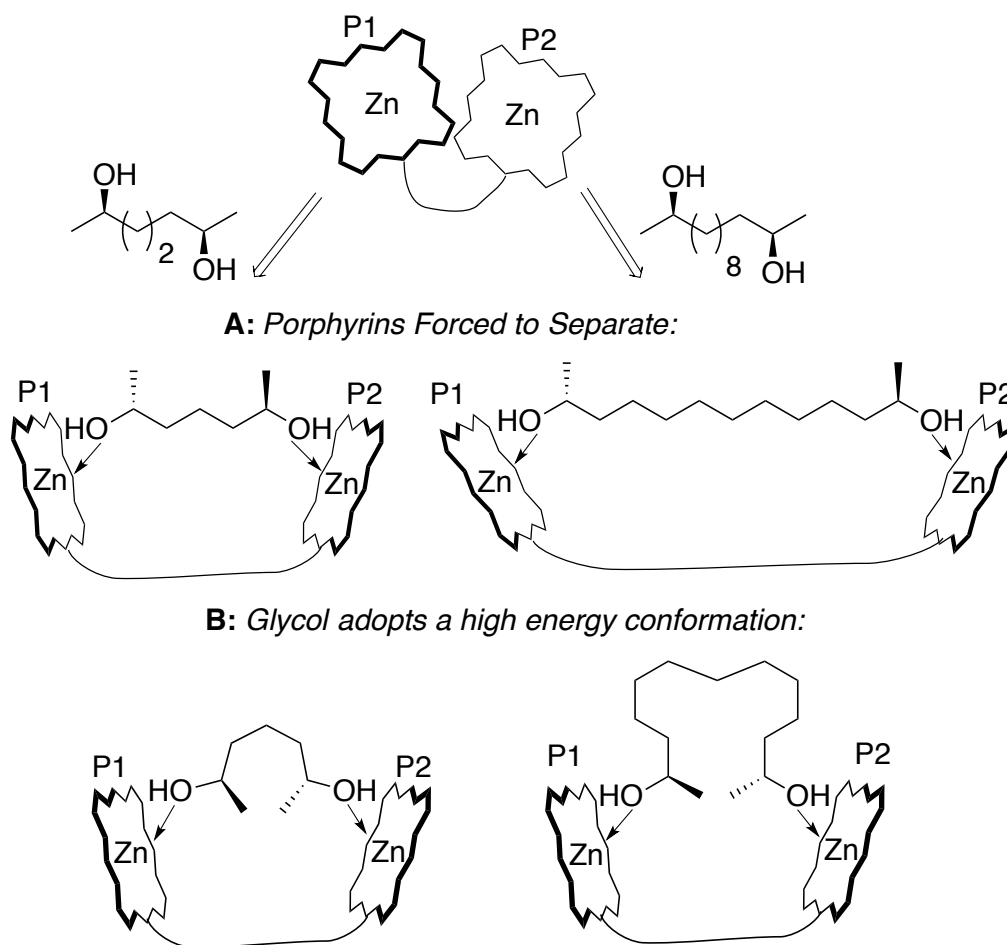
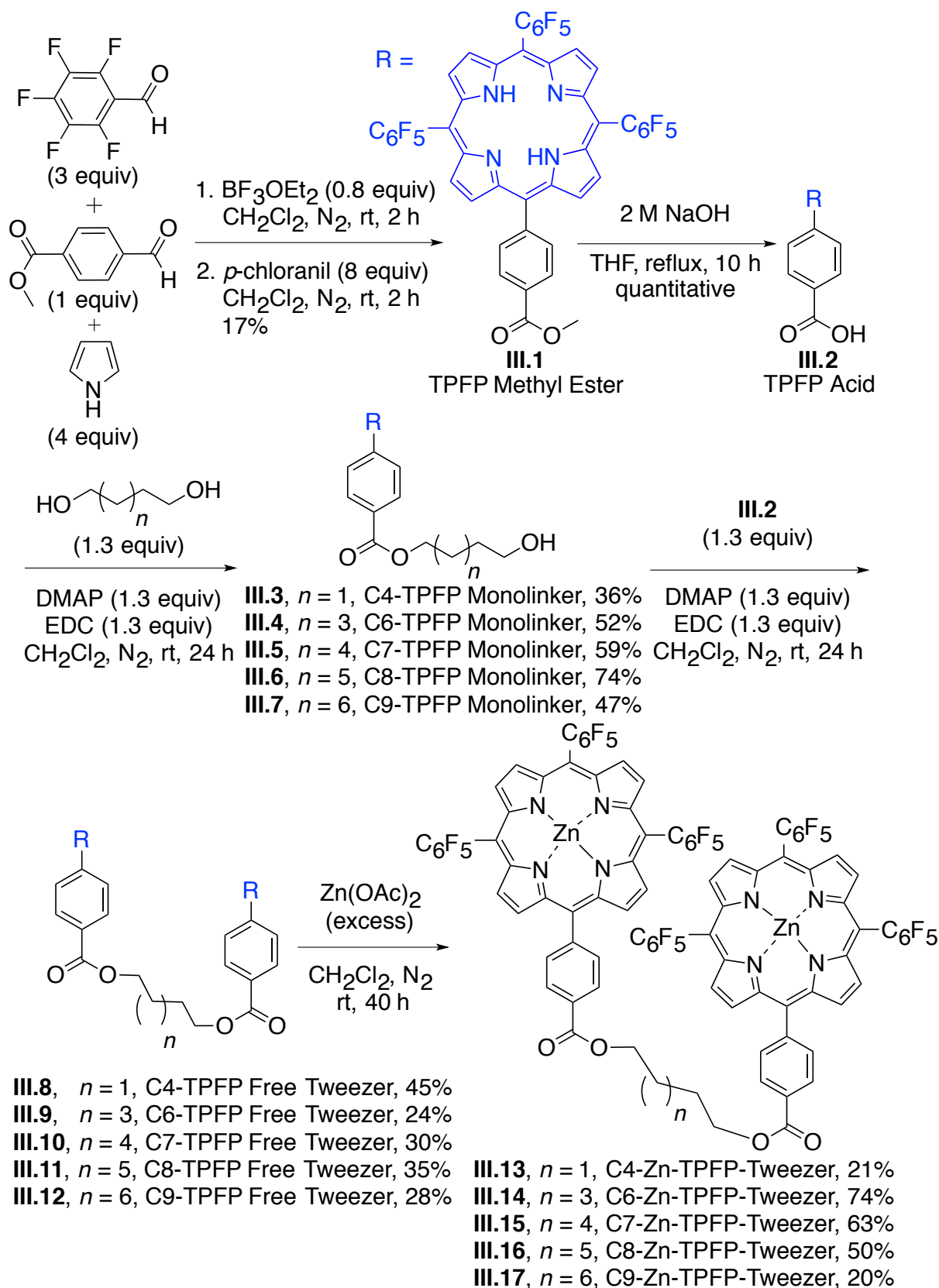


Figure III.9: The possible binding modes of a 1,*n*-glycol with C5-Zn-TPFP-Tweezer. As the number of methylenes separating the hydroxyls increases, either the porphyrins are forced farther apart (**A**) or the glycol must wrap into a high energy conformation (**B**). The unfavorable conformation of either the tweezer or the glycol could be causing the ECCD results that do not fit the mnemonic.

ECCD results. If this hypothesis was correct, then a tweezer with a shorter linker would be less reliable than the original tweezer as shortening the linker would further reduce the size of the binding pocket and binding of the glycol would be less favorable. On the other hand, a tweezer with a longer linker should have a larger binding pocket, be more accommodating of the long

chain glycols and the ECCD results should be more reliable. The plan for new tweezers was for them to have linkers from three methylene units to nine methylene units (including five methylene linker of the original tweezer, C5-Zn-TPFP-Tweezer).

The synthesis of the TPFP Tweezers followed the literature reported procedure for C5-Zn-TPFP-Tweezer (Scheme III.1).⁸ The TPFP methyl ester (**1**) was obtained from an acid catalyzed condensation of pentafluorobenzaldehyde, pyrrole and 4-formylmethylbenzoate in fairly good yield for a porphyrin condensation (17% yield). Hydrolysis of the ester under basic conditions provided the TPFP acid (**2**) in quantitative yield. The EDC mediated coupling of the TPFP Acid (**2**) with the appropriate terminal diol provided the C4 and C6-C9 monolinkers (**3-7**) and subsequent EDC coupling of the C4-C9 monolinkers with the TPFP acid yielded the C4 and C6-C9 free tweezers (**8-12**). The yields for the second EDC coupling were fairly low. This was expected as the initial couplings to the monolinkers gave moderate yields. Typically, the second coupling has lower yields than the first coupling. Zincation of the free tweezers with zinc II acetate generated the (C4 and C6-C9)-Zn-TPFP-Tweezers (**13-17**) in rather low yields for some cases. This is likely due to the generation of acetic acid upon zincation of the tweezer as acid is known to cause demetallation of metalloporphyrins. Simultaneously, Dr. Li synthesized the C3-Zn-TPFP-Tweezer following the same procedure with 1,3-propane diol. These tweezers were then used for ECCD analysis of the 1,*n*-glycols.



Scheme III.1: Synthesis of the C4 and C6-C9-Zn-TPFP-Tweezers.

III.4: ECCD Study of the 1,*n*-Glycols Using the Modified Zn-TPFP-Tweezers

For the ECCD study, each titration was conducted in hexanes at 0 °C with 2 μM and varied equivalents of the glycol. Summarized in the following tables (Table III.1/2) are the results for the study. The ECCD results that do not match the mnemonic are highlighted in red. Interestingly, the only tweezer of the series that provided the expected ECCD result for every glycol tested was C3-Zn-TPFP-Tweezer therefore, shortening of the linker leads to more stable complexes for all of the long chain glycols. The C3-Zn-TPFP-Tweezer was reported as the optimal tweezer for an ECCD protocol of 1,*n*-glycols and a mnemonic was established for 1,*n*-glycols using this tweezer.⁶¹ The mnemonic and a new line of reasoning to explain the success of this tweezer will be discussed in due course. The ECCD results for the longer linker tweezers did not support our original hypothesis however, there were some interesting results and observations made during the course of the study. Counterintuitively:

- the short chain glycols were the most problematic
- the long chain glycols consistently generated ECCD signals of the correct sign.
- K_{as} for the long glycols with C3 tweezer were $\sim 10^4$ M
- K_{as} for the long chain glycols with C8 and C9 tweezer were $\sim 10^6$ M

The shorter chain glycols (1,3 - 1,6) were the most problematic (Table III.1) for all the tweezers except C3-Zn-TPFP-Tz. ECCD analysis of (2*S*, 4*S*)-pentane diol generated the expected negative signal with only the C3 and C4 tweezers, the tweezers with the shortest linkers. Increasing the length of the linker made ECCD less reliable for the short chain glycols as inconsistencies were observed for the 1,3 - 1,6 glycols with various tweezers. These results suggest that the complexes of the tweezers with longer linkers and short chain glycols are less

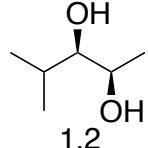
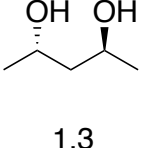
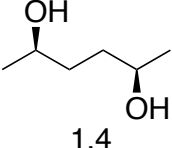
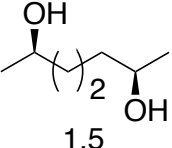
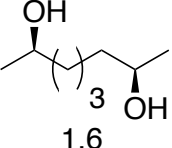
Tweezer	Glycol				
	 1,2	 1,3	 1,4	 1,5	 1,6
C3	425 (+102) 413 (-77) A = +179	423 (-38) 412 (+37) A = -73	424 (+72) 414 (-66) A = +138	423 (+136) 414 (+100) A = +236	422 (+322) 415 (-203) A = +525
C4	424 (+92) 412 (-115) A = +207	426 (-23) 417 (+19) A = -42	429 (-21) 419 (+36) A = -57	No ECCD	428 (-18) 421 (+155) 413 (-58)
C5	425 (+128) 413 (-96) A = +224	424 (+81) 419 (-71) A = +152	424 (+205) 413 (-163) A = +368	424 (+174) 413 (-135) A = +309	426 (-70) 416 (+53) A = -123
C6	424 (+112) 411 (-75) A = +187	423 (+303) 414 (-203) A = +506	423 (+69) 413 (-55) A = +124	423 (+54) 414 (-89) A = +143	425 (-148) 414 (+222) A = -370 ^a
C7	425 (+58) 410 (-16) A = +74	423 (+300) 414 (-193) A = +493	425 (+52) 414 (-48) A = +100	423 (+161) 414 (-87) A = +258	425 (-247) 416 (+187) A = -434 ^a
C8	424 (+25) 413 (-13) A = +38	422 (+118) 415 (-131) A = +249	423 (+64) 413 (-43) A = +107	424 (-50) 417 (+81) A = -131	422 (+87) 415 (-43) A = +130
C9	424 (+135) 412 (-76) A = +211	423 (+286) 414 (-224) A = +510	423 (+66) 413 (-48) A = +114 ^b	424 (-90) 417 (+147) 410 (-21)	423 (+64) 416 (-37) A = +101

Table III.1: Summary of ECCD results for the 1,2 - 1,6-glycols with C3 - C9-Zn-TPFP-Tweezers. Results in red do not match the sign predicted by the mnemonic. Each entry in the table gives the first Cotton effect, λ nm ($\Delta\epsilon$), second Cotton effect λ nm ($\Delta\epsilon$) and overall amplitude (A). All measurements: hexanes, 0 °C, 2 μ M tweezer, 40 equivalents glycol. a: 10 equivalents glycol. b: 20 equivalents glycol.

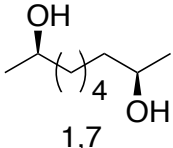
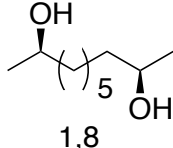
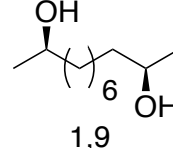
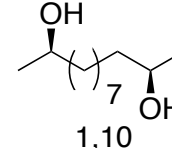
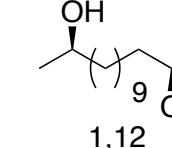
	 Glycol Tweezer 1,7	 1,8	 1,9	 1,10	 1,12
C3	423 (+152) 414 (-142) A = +294	426 (+156) 416 (-197) A = +353	424 (+400) 415 (-351) A = +751	427 (+408) 416 (-326) A = +734	424 (+193) 415 (-123) A = +316
C4	423 (+80) 417 (-53) A = +133	425 (+129) 417 (-110) A = +239	425 (+90) 417 (-72) A = +162	425 (+142) 416 (-116) A = +258	424 (+82) 415 (-51) A = +133
C5	422 (-237) 416 (+199) A = +436	426 (+146) 415 (-140) A = +286	423 (+172) 414 (-130) A = +302	425 (+314) 415 (-177) A = +491	430 (-91) 423 (+506) 414 (-171)
C6	422 (-236) 416 (+288) A = -524	422 (+161) 413 (-71) A = +232	429 (+137) 409 (-80) A = +217	423 (+107) 415 (-99) A = +206	423 (+84) 417 (-57) A = +141
C7	423 (+294) 414 (-262) A = +556 ^b	422 (+184) 416 (-193) A = +377	422 (+306) 415 (-238) A = +544	424 (+501) 416 (-279) A = +780	422 (+127) 416 (-105) A = +232 ^b
C8	424 (+186) 415 (-126) A = +312	423 (+1383) 416 (-1051) A = +2434	423 (+1130) 416 (-876) A = +2006	423 (+511) 413 (-289) A = +800	423 (+433) 416 (-311) A = +744
C9	424 (+613) 415 (-331) A = +944	423 (+2311) 416 (-1780) A = +4091	423 (+2028) 416 (-1556) A = +3584	423 (+902) 416 (-781) A = +1683	422 (+1015) 415 (-829) A = +1844

Table III.2: Summary of ECCD results for the 1,7 - 1,10 and 1,12-glycols with C3 - C9-Zn-TPFP-Tweezers. Results in red do not match the sign predicted by the mnemonic. The results with exceptionally large amplitudes are highlighted in blue. Each entry in the table gives the first Cotton effect, λ nm ($\Delta\epsilon$), second Cotton effect λ nm ($\Delta\epsilon$) and overall amplitude (A). All measurements: hexanes, 0 °C, 2 μ M tweezer, 40 equivalents glycol. a: 10 equivalents glycol. b: 20 equivalents glycol.

stable. To bring the porphyrins in close enough proximity to bind to the hydroxyl groups of the short chain glycols, the methylene chain of the tweezer is likely adopting a high energy, non-linear conformation which results in an unfavorable, high energy complex (Figure III.10). These high energy, less stable complexes could be accessing a number of different ECCD active complexes leading to ECCD signals of the incorrect sign.

The ECCD results for the complexes of the longer chain glycols (1,7 - 1,12) with all of the tweezers provided bisignate curves of the predicted sign, with the exception of two complexes, C6 Tweezer with 1,7-glycol and C5 Tweezer with 1,12-glycol. This was a surprising result. Particularly for the long chain glycols with the tweezers of short linker lengths. Initially, it was thought that upon binding with the tweezer, the glycols would be forced to adopt a high energy, non-staggered conformation thereby creating high energy, unstable complexes (Figure

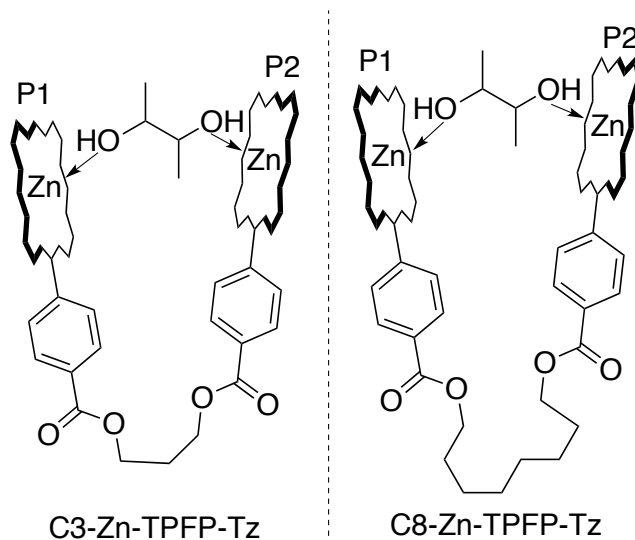


Figure III.10: Complexes of a 1,2-glycol with C3- and C8-Zn-TPFP-Tweezer. It is thought that the linker of C8-Zn-TPFP-Tweezer will have to enter a high energy conformation to bind with the glycol.

III.9 B). Therefore, it was expected that the ECCD analysis of the longer chain glycols with short linker tweezers would be inconsistent. However, this was shown to be incorrect.

Furthermore, for the C8 and C9 tweezers, ECCD analysis of the 1,8 - 1,12 glycols resulted in surprisingly large amplitudes, at times in excess of 1000. This indicates that the longer linker of the tweezer promotes binding with the long chain glycols, thus supporting our original hypothesis that more flexibility in the tweezer would favor complex formation with the long chain glycols by creating a larger binding pocket. However, the inconsistencies observed with the short chain glycols eliminates the C6 - C9 tweezers as reliable host molecules for the determination of configuration for 1,*n*-glycols.

Intrigued by the dramatic ECCD signals of the C8- and C9-Zn-TPFP-Tweezers with the 1,8 - 1,12-glycols, a UV-Vis analysis of each complex was undertaken. The purpose of the UV-Vis analysis was to elucidate the binding constants for each complex with the hypothesis that the complexes of C8- and C9-Zn-TPFP-Tweezers with the 1,8 - 1,12-glycols had significantly larger binding constants. The large binding constant would indicate a tight and rigid complex which would reduce the number of ECCD complexes contributing to the observed signal and could be the underlying cause of the intense signals. In the following tables, (Table III.3/4) the binding constant data is summarized.

These binding constant calculations provided some interesting observations. Firstly, the 1,*n*-glycol with C5-, C6- or C7-Zn-TPFP-Tweezer consistently produced binding constants in the range of $1 - 5 \times 10^5$ M. This value correlates well with the literature reported K_a for C5-Zn-TPFP-Tweezer with a vicinal diol (1.5×10^5 M).⁸ However, other tweezers of the series (C3-, C4-, C8- and C9-), showed different trends. The observed binding constants with these tweezers

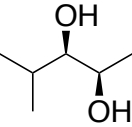
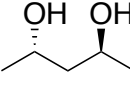
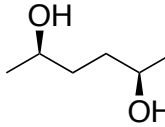
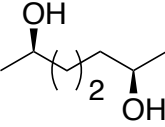
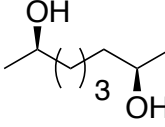
Tweezer	Glycol				
	 1,2	 1,3	 1,4	 1,5	 1,6
C3	A = +179 $K_a = 21020 \pm 2480$ $R^2 = 0.99146$	A = -73 28439 ± 3142 0.99631	A = +138 ND	A = +236 15678 ± 2946 0.99878	A = +525 6410 ± 287 0.99744
C4	A = +207 50603 ± 17679 0.93351	A = -42 33546 ± 5014 0.97485	A = -57 47654 ± 2182 0.99942	No ECCD 7144 ± 93 0.99979	Trisignate 5094 ± 207 0.99886
C5	A = +224 98587 ± 7572 0.99766	A = +152 51611 ± 1850 0.99929	A = +368 ND	A = +309 24985 ± 1609 0.98852	A = -123 12333 ± 363 0.9992
C6	A = +187 32189 ± 2886 0.99466	A = +506 5004 ± 528 0.99304	A = +124 9312 ± 911 0.99795	A = +143 53745 ± 4565 0.9957	A = -370 ^a 20344 ± 1339 0.997
C7	A = +74 6013 ± 922 0.98012	A = +493 37737 ± 2804 0.99306	A = +100 15829 ± 926 0.99579	A = +258 34729 ± 3317 0.99591	A = -434 ^a 7783 ± 703 0.99406
C8	A = +38 16910 ± 927 0.99869	A = +249 97270 ± 12273 0.99148	A = +107 23175 ± 5390 0.99977	A = -131 71076 ± 12027 0.98957	A = +130 13497 ± 494 0.99844
C9	A = +211 15218 ± 1064 0.993	A = +510 8430 ± 158 0.99966	A = +114 ^b 6198 ± 466 0.99299	Trisignate 43065 ± 9464 0.96577	A = +101 12045 ± 315 0.99772

Table III.3: Binding constants for complexes of the 1,2 - 1,6 glycols with the C3 - C9 TFP Tweezers. Each entry in the table provides the overall ECCD amplitude, binding constant with error and the R^2 . Red entries did not match the ECCD sign predicted by the mnemonic. ND = Not Determined. All measurements were taken at room temperature in hexanes. The binding constants were determined using KaleidaGraph and Equation III.1 (See experimental).

Glycol	1,7	1,8	1,9	1,10	1,12
Tweezer					
C3	A = +294 $K_a = 4612 \pm 182$ $R^2 = 0.99849$	A = +353 3817 ± 290 0.99312	A = +751 4746 ± 198 0.99841	A = +734 2017 ± 151 0.99615	A = +316 9888 ± 154 0.99962
C4	A = +133 9111 ± 1476 0.9832	A = +239 18262 ± 450 0.99981	A = +162 5220 ± 189 0.99907	A = +258 3068 ± 231 0.99755	A = +133 8199 ± 733 0.99709
C5	A = +436 25866 ± 1600 0.99619	A = +286 12846 ± 421 0.99911	A = +302 29516 ± 2480 0.99367	A = +491 5853 ± 570 0.98999	Trisignate 16698 ± 1413 0.99276
C6	A = -524 28801 ± 1430 0.99776	A = +232 21064 ± 761 0.9987	A = +217 34631 ± 791 0.99927	A = +206 40546 ± 821 0.99953	A = +141 33257 ± 1843 0.99707
C7	A = +556 ^b 32218 ± 1878 0.99529	A = +377 24475 ± 2532 0.98937	A = +544 18138 ± 1051 0.99686	A = +780 24758 ± 686 0.99918	A = +232 ^b 38503 ± 2924 0.99559
C8	A = +312 220340 ± 11501 0.99709	A = +2434 288210 ± 23944 0.99253	A = +2006 600300 ± 25609 0.99795	A = +800 691360 ± 14374 0.99959	A = +744 224070 ± 4712 0.99945
C9	A = +944 264760 ± 9809 0.99725	A = +4091 658170 ± 29435 0.99767	A = +3584 586640 ± 10582 0.99957	A = +1683 761990 ± 47790 0.9961	A = +1844 187670 ± 15127 0.99832

Table III.4: Binding constants for complexes of the 1,7 - 1,10 and 1,12 glycols with the C3

- C9 TFP Tweezers. Each entry in the table provides the overall ECCD amplitude, binding constant with error and the R^2 . Red entries did not match the ECCD sign predicted by the mnemonic and blue entries are ECCD measurements of large amplitude. All measurements were taken at room temperature in hexanes. The binding constants were determined using KaleidaGraph and Equation III.1 (See experimental).

showed a correlation of K_a with the length of the glycol. For the complexes of C8- and C9-Zn-TPFP-Tweezers with the shorter chain glycols (1,2- through 1,6-) the binding constants were in the order of 10^5 M which agrees well with the literature reported value. However, for the longer chain glycols (1,7- through 1,12-) the K_a values increase 10 fold to 10^6 M. Interestingly, the complexes of C8- and C9-Zn-TPFP-Tweezers with these diols provided the most intense ECCD signals. The larger binding constants suggest that a tighter, more rigid complex has formed which would limit the number of conformations that the complex could access. A small number or possibly a single conformation of the complex would be favored. Thus, this could explain the intense ECCD signals.

The C3- and C4-TPFP-Tweezers also demonstrate interesting behaviors. For short chain diols (1,2- to 1,4-diols) the binding constants are comparable to the literature reported complex, approximately 2×10^5 M. However, the binding constants fall 10 fold to values between $1 - 5 \times 10^4$ M, for the longer glycols. This result is somewhat surprising. Smaller binding constants suggest weak complex formation. It is expected that these complexes would have greater degrees of freedom and be able to sample a number of ECCD active complexes thus producing poor ECCD signals. Yet, these small binding constants are observed with the most reliable and consistent tweezer of the series. This observation for the C3-Zn-TPFP-Tweezer needs further explanation but could be the result of a different binding mode, which will be discussed.

III.5: Proposal of a New Binding Mode and a Mnemonic for the 1,*n*-glycols

The necessity to propose a new binding mode was the consequence of several observations from both the ECCD and UV-Vis titrations. During the ECCD titrations, it was noted that the long chain glycols (1,8 - 1,10 and 1,12-diols) exhibited intense ECCD response. The original binding mode proposed that the glycol could be forcing the porphyrins away from one another to form a binding pocket large enough for the lowest energy, staggered conformation of the glycol (Figure III.9 B). If this was the active binding mode, as the length of the diol increased, the distance between the porphyrins would also increase. The amplitude of a ECCD signal is inversely proportional to the distance between the chromophores to the sixth power (See Chapter I, Equation I.). Therefore, as glycol length and the distance between the chromophores increases, the ECCD amplitude should decrease making this binding mode unlikely. It should be noted that the angle between the porphyrins will also influence the intensity of the ECCD signal. ECCD amplitudes maximize near an angle of 70° therefore, if the angle between the porphyrins approaches 70° as the length of the glycol increases, the amplitude of the ECCD would also increase. However, the distance between chromophores has a greater impact on the amplitude. Since the 1,9-glycol generates an ECCD signal with larger amplitude than the 1,2-diol, the chromophores must remain in close proximity to one another with the long chain glycol bound.

The other binding mode previously discussed would require the glycol to wrap into a high energy, non-linear, conformation to fit into the binding pocket of the tweezer (Figure III.9 B). This was also ruled out based on the intensity of the ECCD amplitudes and the binding constants of the glycols with the tweezer. If this is the operational binding mode it would be

expected that the binding constants for the glycols should become smaller as the glycol becomes longer. The longer glycols have more methylene units to rotate into high energy conformations in order for the glycol to fit into the binding pocket. This would create an unfavorable and high energy conformation of the diol and the complex therefore, it was hypothesized that weaker binding constants for the longer chain glycols would be observed. Additionally, weaker binding should create smaller ECCD amplitudes as the complex has more degrees of freedom. As discussed previously, UV-Vis analysis indicates that the binding constants for the shorter glycols (K_a for 1,3-diol = 1.2×10^5 M) are 10-fold larger than the long chain glycols (K_a for 1,7-diol = 2.7×10^4 M). At first glance, this would seem to favor the proposed binding mode that requires the glycol to adopt a non-linear conformation (Figure III.9 B) as the binding constants do decrease. However, there is little change of K_a from the 1,7-glycol to the 1,12-glycol ($K_a = 2.1 \times 10^4$ M) even though an additional six methylene units have been added to the glycol. Furthermore, the long chain glycols provided intense ECCD signals. Therefore, both of the previously proposed binding modes (Figure III.9 A and B), could be eliminated as the binding constants remain relatively constant and the ECCD amplitudes are large for the long chain glycols.

The UV-Vis titrations provided another line of reasoning to further substantiate the necessity of a new binding model for C3-Zn-TPFP-Tweezer. When a substrate binds with the Zn-Tweezers, typically a red shift of the porphyrin Soret band is observed. The extent of the red shift is the result of two competing factors. One is the red shift from the donation of electrons from the coordinating functional group into the LUMO of the metal center of the porphyrin. The second is a blue shift caused by bringing the porphyrins in close proximity of one another.

When the porphyrins are very close, say bound to 1,2-diaminoethane, an overall small red shift of the porphyrin Soret band is observed (See Chapter 2, Figure II.9). If the porphyrins have greater distance between them, an overall a large red shift is observed. For a single class of molecules, the red shift remains the same as the same types of functional groups are participating in the binding interactions; all amines should cause a 12 nm red shift when binding to Zn-TPP. But, the overall red shift of the Soret band depends on the distance between the porphyrins.

A report by Nakanishi and coworkers in 1998 disclosed a UV-Vis study of the C5-Zn-TPP-Tweezer with terminal diamines of varied length.⁶² They found that as the length of the diamine increased, the extent to which the tweezer Soret band red shifted increased in a linear fashion (Figure III.11, blue triangles). In other words, for every methylene unit added to the diamine backbone, the Soret band would red shift approximately 30 wavenumbers more. Based on these results, they proposed that there is a linear dependence between the number of methylene units of the diamine and the distance between the porphyrins. The distance between the porphyrins increases the same amount for each methylene added into the diamine chain so the blue shift decreases the same amount each time a methylene unit is added into the diamine backbone. Thus, the Soret band would shift the same amount (30 wavenumbers) each time a methylene was added to the diamine chain. These observations lead to the proposal of the binding mode in Figure III.9 A.

A UV-Vis study of C3-Zn-TPFP-Tweezer with terminal diamines and chiral glycols was conducted in the same fashion. For the terminal diamines, a linear dependence between the shift of the Soret band and the length of the diamine was again observed (Figure III.11 red

squares). This would suggest that same binding mode is operational for C5-Zn-TPP-Tweezer and C3-Zn-TPFP-Tweezer with the diamine substrates. But, for the 1,*n*-glycols, an exponential relationship between glycol length and the Soret band red shift was observed (Figure III.11 green triangles). For the long chain glycols (1,6- to 1,12-) there is a change in the Soret band

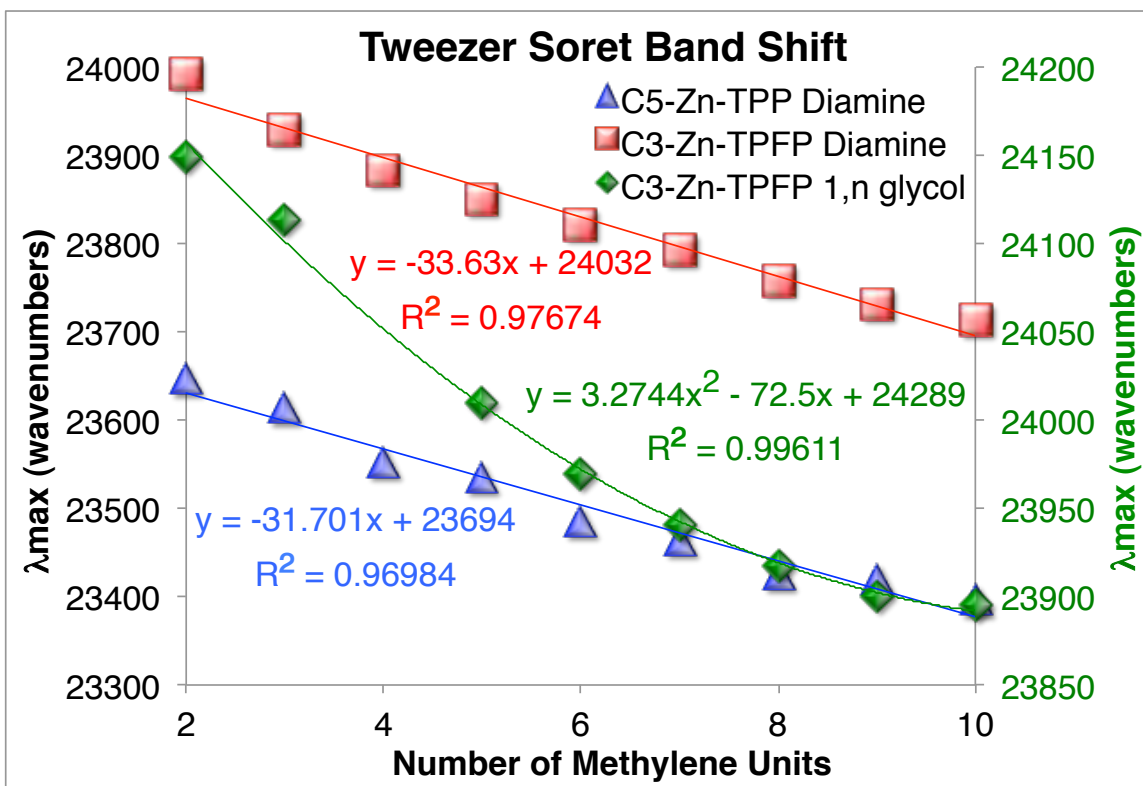


Figure III.11: Graphical representation of the change of absorbance for the tweezer Soret band relative to the number of carbons between the binding functionalities. Blue Triangles: C5-Zn-TPP-Tweezer with the terminal diamines showing linear dependence.⁶² Red squares: C3-Zn-TPFP-Tweezer with the terminal diamines showing linear trend. Green diamonds: C3-Zn-TPFP-Tweezer with the chiral 1,*n*-glycols show a polynomial trend where the shift is smaller with longer glycols. UV-Vis measurements for C3-Zn-TPFP-Tweezer taken in hexanes at room temperature.

shift (15 wavenumbers per methylene unit) however, it is smaller than the shift observed for the diamines suggesting that the porphyrins remain closer in space when a complex with a long chain glycol is formed in comparison to the complex with a long chain diamine.

In all, the long chain glycols exhibit large ECCD amplitudes and in UV-Vis small shifts of the porphyrin Soret band are observed. These observations suggest that the porphyrins remain close in space when the C3-Zn-TPFP-Tweezer/glycol complexes have formed without forcing the glycol into an unfavorable, high energy conformation. The binding models in Figure III.9 A and B cannot reasonably explain these observations so, a new binding model was developed.

The binding model in Figure III.9 A where the porphyrins approach the chiral molecule from the ends of the molecule, perpendicular to the backbone of the substrate, and the porphyrins are forced apart in such a way that the guest can fit into the binding pocket will be known for the remainder of these discussions as “head-on” binding. When this mode of binding is operational, the increasing distance between the chiral centers also increases the distance between the porphyrins. By definition, as the distance between the porphyrins increases, decreased ECCD amplitudes should be observed as ECCD is inversely proportional to the distance between chromophores to the sixth power (Figure III.12 A).

Figure III.12 B depicts the newly proposed binding model called “side-on” binding. For this binding mode, the porphyrins approach the chiral centers parallel to the methylene backbone of the substrate. This approach is thought to explain the ECCD and UV-Vis observations as the distance between the porphyrins will not greatly change as the diol chain becomes longer. To accommodate the longer chain glycols in this binding model, the porphyrins rotate away from one another as though the porphyrins are attached to a hinge that

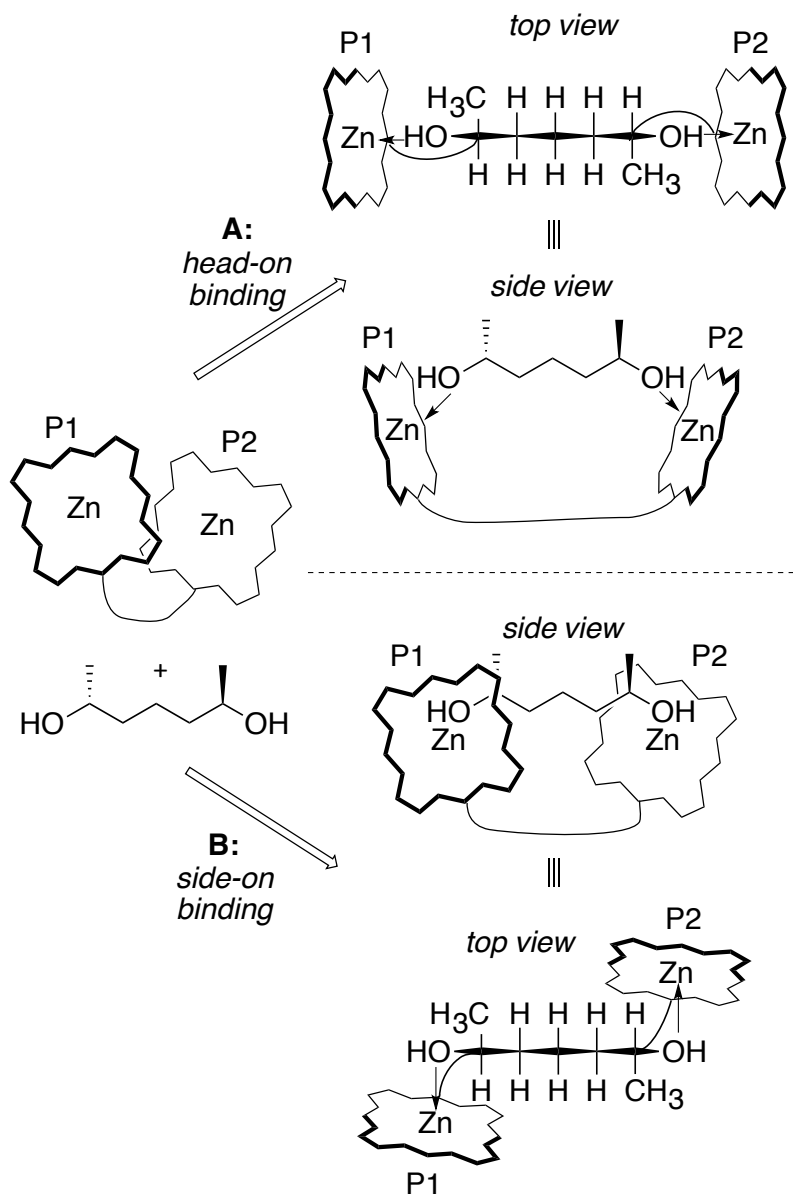


Figure III.12: Binding modes for porphyrin tweezers. **A:** The original “head-on” binding where the porphyrins bind perpendicular to the glycol backbone. **B:** The proposed “side-on” binding where the porphyrins approach the glycol parallel to the methylene backbone.

allows the plane of the porphyrins slide across one another. Therefore, as the glycol chain becomes longer, the angle between the porphyrins should increase. For vicinal diols, as the

angle between the chromophores increases from 0° , the ECCD amplitude increases and eventually reaches a maximum amplitude around 70° . The amplitudes then decrease from 70° to provide no ECCD signal again at 180° . A similar trend is proposed for this binding model. As the glycol chain length increases, so should the angle between the chromophores and the ECCD signal is expected to increase as well. If this binding model is operational, the combination of the increasing angle and the close proximity of the porphyrins would explain the large ECCD amplitudes for the long chain glycols (1,6- to 1,12-).

Figure III.13 provides minimized structures for the 1,7-glycol bound to two Zn-TPFP-Me Ester porphyrins in either the head-on or side-on binding mode. The distance between the porphyrins in each of the complexes can be easily seen from the top view of each complex as indicated by the dashed black line (Figure III.13 A and B). The dashed blue lines show the coordination of the hydroxyls to the zinc centers of the porphyrins. As predicted, the distance between the porphyrins is much larger for the complex in the head-on binding mode. To gain a feel for the angle between the porphyrins, the side view for each complex is also provided (Figure III.13 C and D). The black dashed line through each of the porphyrins represents the major electric transition dipole moment that participates in the coupling interaction to provide the ECCD signal. The angle between the chromophores for the side-on binding mode is larger than the angle in the head-on binding mode. The porphyrins in the side-on mode of binding are closer together and the angle between them is larger so, by definition, the ECCD amplitude would be larger for the side-on binding mode than if the glycol was bound to the porphyrins in the head-on binding model. The side-on binding model can explain the large ECCD amplitudes.

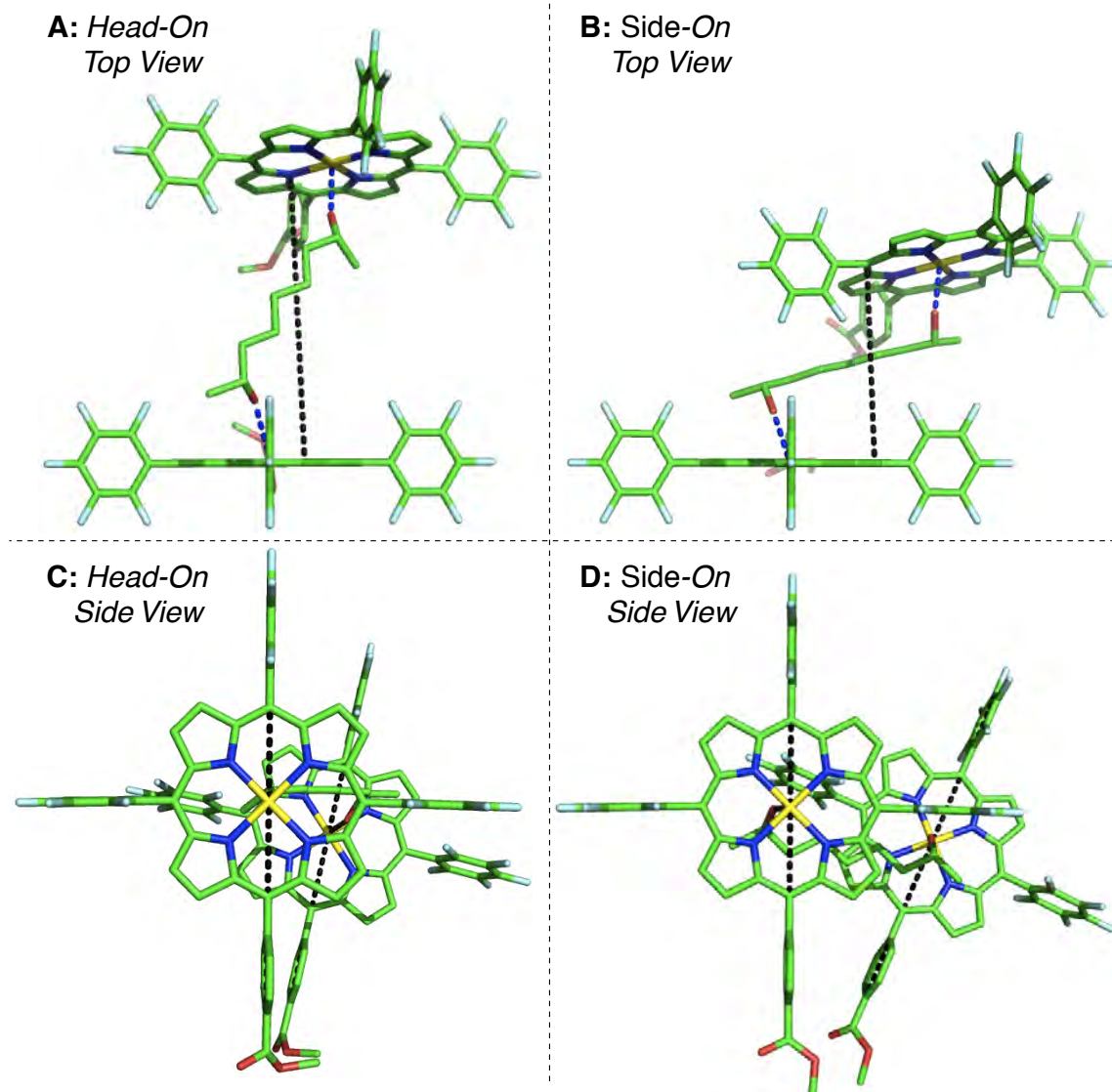


Figure III.13: Different views of the head-on and side-on binding models for 2*R*,7*R*-octanediol with two Zn-TPFP-Me ester porphyrins. **A/B:** The top view of the head-on binding mode and side-on binding modes respectively. The dashed black lines show the distance between the porphyrins and the dashed blue lines indicate coordination between the hydroxyls and zinc centers. **C/D:** The side view of the head-on binding mode and side-on binding modes respectively. The dashed black lines represent the electric transition dipole moments of the porphyrins. The shorter distance and larger angle between porphyrins in the side-on binding would produce larger ECCD signals.

With a binding model that explains the observed ECCD signals, next a mnemonic for 1,*n*-glycols was developed. The mnemonic for the vicinal diols was used as starting point.⁸ As with the vicinal diols, each of the hydroxyl centers of the 1,*n*-glycol was considered as an independent chiral site. At each of the chiral centers, the porphyrin would approach the hydroxyl from the opposite face of the large group (methyl for the 2*R*,5*R*-hexanediol in Figure III.14 A). The porphyrin would then rotate to minimize steric repulsion with the methylene chain (shown in green in the Newman projection) by sliding toward the smaller hydrogen. For 2*R*,5*R*-hexanediol, this results in a clockwise helicity of the porphyrins and a positive ECCD was observed. This applies to all glycols with an even number of methylene units between the glycols (even glycols).

Figure III.14 B shows the mnemonic for the glycols with an odd number of methylene units between the hydroxyls (odd glycols), such as 2*R*,6*R*-heptanediol. For the odd glycols, the most stable conformation of the glycol would result in the hydroxyls being situated on the same face of the methylene chain. If binding to this conformation of the diol was possible, the porphyrins would have to approach the glycol on the same side of the methylene backbone and no ECCD would be expected. Therefore, for an ECCD active complex with an odd glycol, a higher energy, staggered rotomer of the glycol is required so that the hydroxyl groups are on opposite sides of the methylene chain. The crystal structure of 2*R*,10*R*-undecane diol, solved by Dr. Li, showed both rotomers of the diol within the same lattice. Therefore, it is possible that this is the conformation of the diol when bound to the tweezer. When the complex forms with an odd glycol, as with the even glycols, the porphyrins approach the hydroxyls *anti* to the methyl group (large group). Then the porphyrin will rotate away from the methylene chain

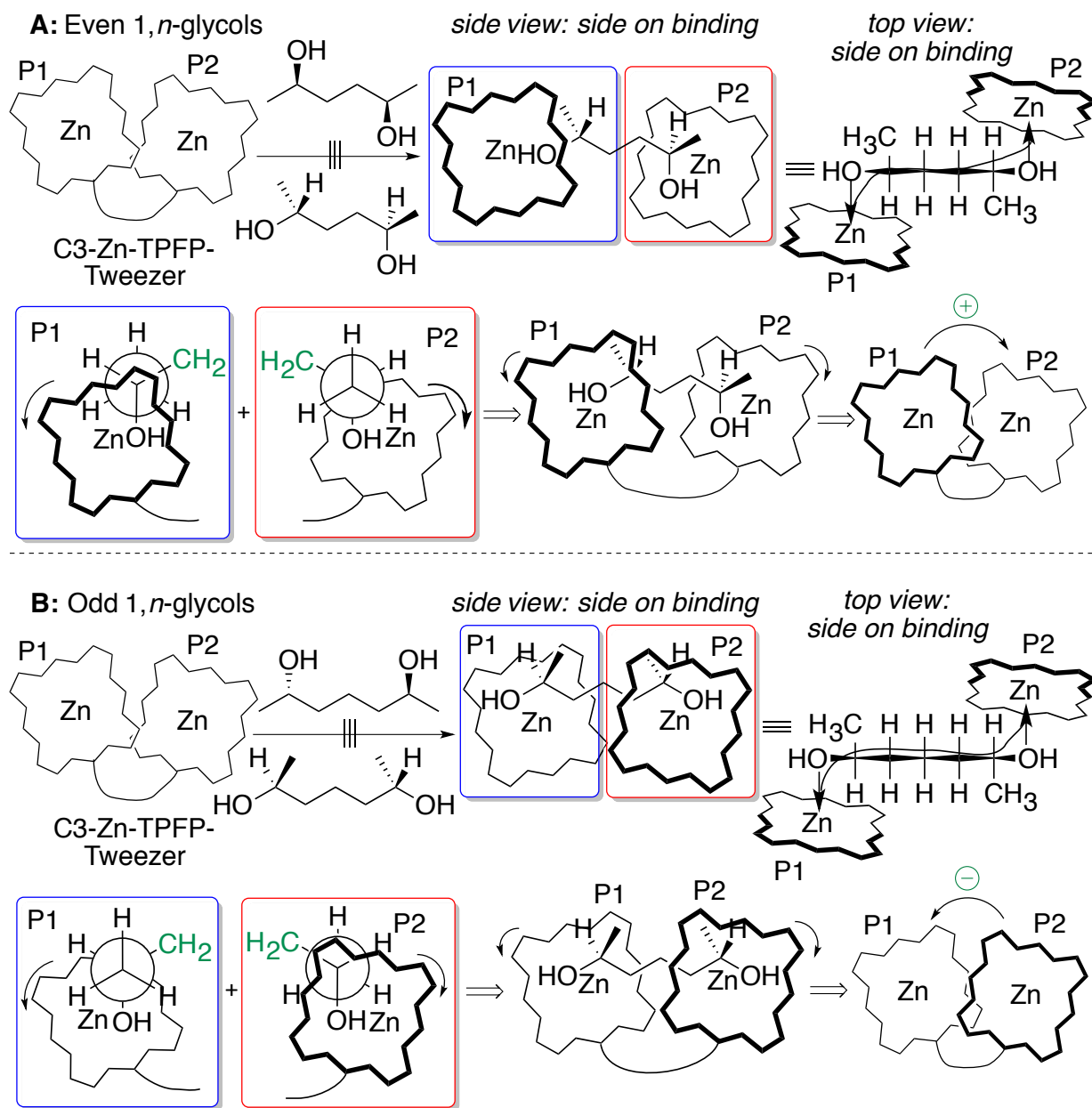


Figure III.14: The proposed mnemonic for 1,*n*-glycols and C5-Zn-TPFP-Tweezer. The porphyrins approach the hydroxyls from the opposite face of the large group (methyl) then will rotate toward the small group (hydrogen). For (*R,R*) glycols a positive ECCD is expected. **A:** A higher energy rotamer of the even glycol binds to the tweezer so that the methyls are *anti*. **B:** For odd glycols, the substrate binds in the lowest energy staggered conformation.

(shown in green in the Newman projection), toward the small hydrogen. For 2*R*,6*R*-heptanediol an overall positive helicity is expected and a positive ECCD is observed.

This mnemonic predicts that any glycol bearing an (*R,R*) configuration would provide a positive ECCD signal and the enantiomeric or pseudo-enantiomeric diols would be expected to generate a negative ECCD signal.

III.5.1: Design and Synthesis of Bis-pyridine (Bpy) Guest Molecules

The new binding model and the mnemonic explain the sign and the intensity of the ECCD signals for the 1,*n*-glycols. However, the correlation of the UV-Vis Soret band shifts with the number of methylene units was yet to be confirmed as a result of the side-on binding model. Therefore, a series of molecules where the binding site is fixed was desired. By fixing the site of the lone pair electrons involved in coordination, the operational binding model could be modeled. It was thought that a series of bis-pyridine compounds would work well for this study (Figure III.15 A). The lone pair electrons of pyridine are set in a fixed location in space and by changing the location of the nitrogen, the binding mode could be changed from head-on with the 4,4'-bispyridines to side-on for the 3,3'-bispyridines (Figure III.15 B). The distance between the nitrogens would be changed by insertion of acetylene units between the pyridines. These rigid bispyridines would have a single binding mode as there are no freely rotatable bonds. In this way the mode of binding as well as the distance between the binding sites would be controlled. Then UV-Vis titrations of these bispyridines with the C3-Zn-TPFP-tweezer and the C5-Zn-TPP-Tweezer would be conducted. If designed correctly, a different

correlation of the Soret band shift with the side-on (3,3'-bpys) and head-on (4,4'-bpys) binding modes should be observed.

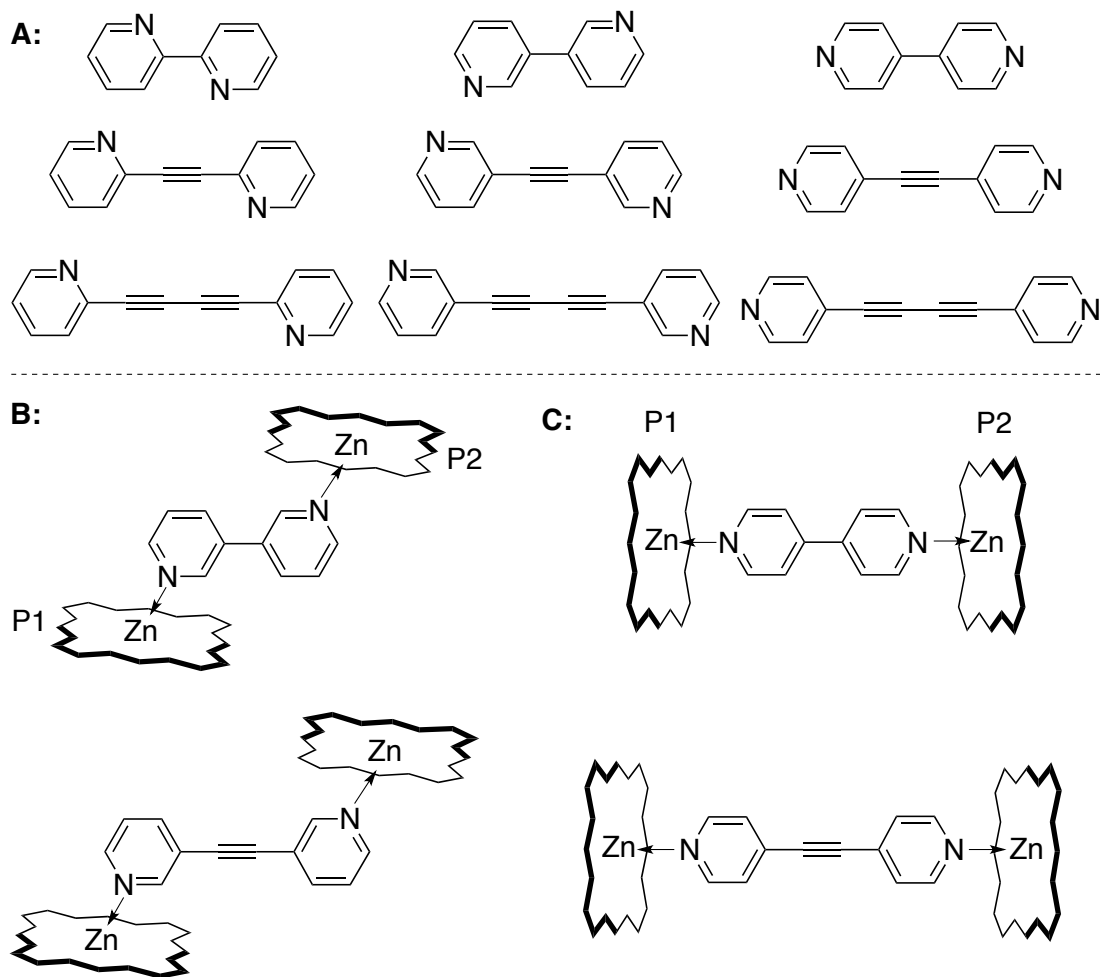
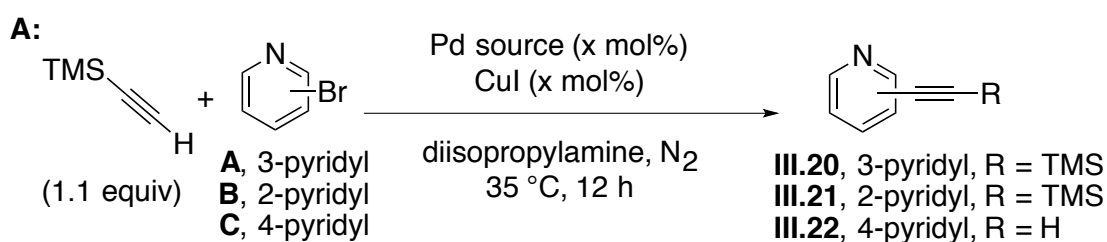


Figure III.15: The bispyridine compounds proposed for a controlled UV-Vis study of tweezer binding modes. **A:** Structures of the target bispyridine compounds. **B:** Tweezer complexes with 3,3'-bispyridines should exhibit the side-on binding mode. **C:** The tweezer complexes with 4,4'-bispyridines should demonstrate the head-on binding mode. The addition of acetylene units between the pyridines is expected to increase the distance between the porphyrins.

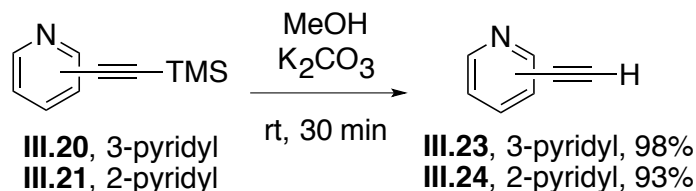
This reaction was attempted several times without successful generation of the desired product. It was thought that generation of the nickel complex was not successful and so the desired product was not obtained. The second attempt using catalytic bis(triphenylphosphine) nickel (II) chloride was successful and provided both bpys albeit in lower yields than reported (Scheme III.2 B).⁶⁴

For the synthesis of the acetylene linked bipys first the 2-, 3- and 4-(2-trimethylsilyl) ethynyl pyridines were generated. Sonogashira coupling of the appropriate bromopyridine and



Entry	Starting Material	Pd source	x	Product	Yield %
1	A	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$	2.5	III.20	0
2	A	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$	5	III.20	0
3	A	$\text{Pd}(\text{PPh}_3)_4$	10	III.20	35
4	B	$\text{Pd}(\text{PPh}_3)_4$	10	III.21	42
5	C	$\text{Pd}(\text{PPh}_3)_4$	10	III.22	17

B:



Scheme III.3: Synthesis of the pyridyl(trimethylsilyl)acetylene precursors for the acetylene linked bispyridines. **A:** Optimization of the Sonogashira coupling conditions.

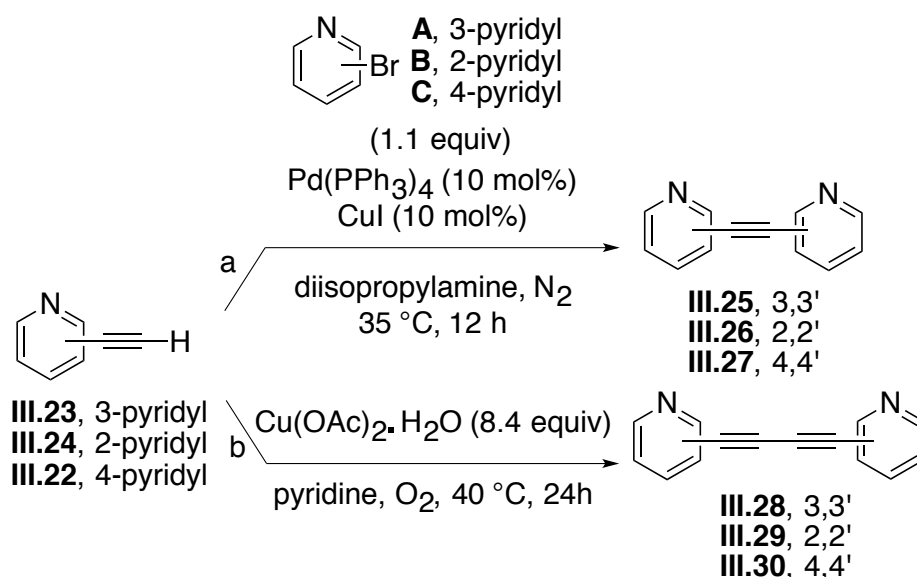
B: TMS deprotection to the free pyridylacetylenes.

TMS-acetylene was employed. The first attempt at the synthesis followed a literature reported protocol using bis(triphenylphosphine)palladium (II) chloride and copper (I) iodide.⁶⁵ This reaction failed however, due to the condition of the palladium catalyst. On the second attempt, palladium-tetrakis(triphenylphosphine) was used with a loading of 2.5 mol% in the presence of 2.5 mol% of copper (I) iodide. This reaction also failed. So, the catalyst loading was increased to 10 mol% and under these conditions the desired products were isolated with moderate yield.

During the synthesis of the 4-(trimethylsilyl)ethynyl pyridine, the trimethylsilyl group was lost therefore, 4-ethynyl pyridine was isolated. To obtain the 2- and 3-ethynyl pyridines, the 2- and 3- (trimethylsilyl)ethynyl pyridines were deprotected with potassium carbonate in methanol (Scheme III.3). Finally, the Sonogashira heterocoupling of 2-, 3- or 4- ethynyl pyridine with the appropriate 2-, 3- or 4-bromopyridine provided the monoacetylene linked bipys (Scheme III.4 A). Subsequently, the copper (II) catalyzed Glaser homocoupling of the 2-, 3- or 4- ethynyl pyridine provided the diacetylene linked bpys (Scheme III.4 B).⁶⁶

III.5.2: UV-Vis Study of Bis-pyridine Guest Molecules with the TPFP Porphyrin Tweezers

With synthesis of the bpys complete, UV-Vis study was initiated. Each of the bispyridines were titrated into a 10^{-6} M solution of either C3- or C5-Zn-TPFP-Tweezer in hexanes at room temperature. The λ_{max} for the porphyrin Soret band was recorded at the saturation point and was plotted against the distance between the nitrogens to gain a better understanding of the Soret band shift dependence on the distance between the pyridine nitrogens.



Entry	Starting Material(s)	Reaction	Product	Yield %
1	III.23, A	a	III.25	12
2	III.24, B	a	III.26	5
3	III.22, C	a	III.27	9
4	III.23	b	III.28	33
5	III.24	b	III.29	45
6	III.22	b	III.30	21

Scheme III.4: Synthesis of the acetylene linked bispyridine compounds. Sonogashira coupling was used for the monoacetylene bispyridines. For the diacetylene bispyridines, Glasier coupling was used.⁶⁶

It was hypothesized that the 2,2'-bpy would exhibit a smaller red shift of the Soret band than the 3,3'-bipy (**III.18**) while 4,4'-bpy (**III.19**) would show the largest red shift. This is due to the distance between the nitrogen atoms in each molecule. The nitrogens are closest together in the 2,2'-bpy therefore, the porphyrins should be closest together and a small shift of the

Soret band is expected. For, the 4,4'-bpy, which disposes the nitrogens farther apart, when bound, the porphyrins will be farther apart and a larger red shift is expected.

Furthermore, the acetylene units between the pyridine moieties will increase the distance between binding sites and a greater red shift is expected with each additional acetylene unit. For example, 3,3'-bpy (**III.18**) should provide a red shift of the Soret band. When a single acetylene unit is added, the distance between the porphyrins increases and the Soret shift with monoacetylene linked 3,3'-bispyridine, **III.26** is expected to be larger than the shift observed for **III.18**. With two acetylene units between the pyridines, the Soret shift of the diacetylene linked 3,3'-bispyridine, **III.29** should be the largest of the series as the distance between the nitrogens and subsequently, the bound porphyrins, is the largest of the series. Figure III.16 summarizes the distances between binding sites and Soret shifts for each titration.

Unfortunately, the 2,2' bispyridines did not exhibit binding with the C3- or C5-Zn-TPFP-Tweezers. The lone pair electrons of these bpps are oriented such that the porphyrin will experience steric interactions with the linker if bound. It is thought that this interaction is large enough to prevent binding with the tweezer.

The 3,3' bispyridines and 4,4' bispyridines did bind and the hypothesized trends of the Soret band shifts were observed. As expected, the 4,4' bispyridines showed larger shifts of the Soret band than did the corresponding 3,3' bispyridines. For example, when the tweezers were titrated with 3,3'-bpy (5.6 Å between nitrogens), the Soret band shifted to ~419 nm and a slightly larger shift to ~420 nm was observed for the titrations with 4,4'-bpy (7.0 Å between nitrogens). This suggests that the porphyrins are closer to one another when bound to the 3,3'-bpy than when bound to the 4,4'-bpy. Being that the 3,3'-bpy binds in a side-on fashion and

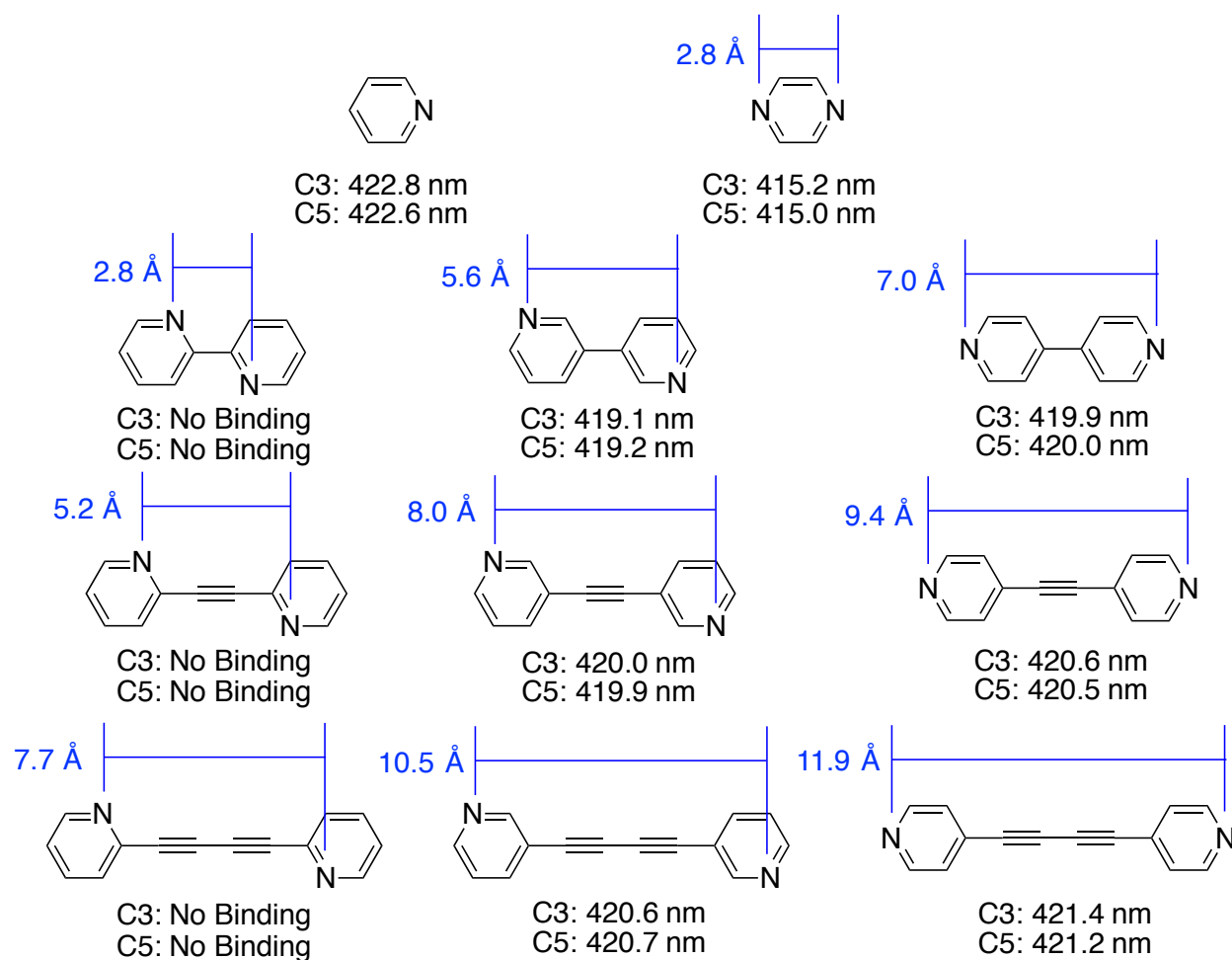


Figure III.16: Summary of the UV-Vis data for the bispyridine titrations with C3- and C5-Zinc-TPFP-Tweezers.

4,4'-bpy binds head-on, this confirms that smaller Soret band shifts are expected for substrates that favor the side-on binding mode.

As expected, the addition of acetylene units between the pyridines of the bispyridine to increase the distance between the nitrogens caused a larger red shift of the Soret band. Binding with pyrazine, which binds head-on due to the orientation of the lone pair electrons, has the smallest distance between the nitrogens (2.8 Å). When titrated into the tweezer solutions, the Soret band shifted to ~415 nm. The 4,4'-bpy, with 7.0 Å between nitrogens, had

a λ_{max} of ~420 nm and the diacetylene linked 4,4'-bispyridine, **III.30**, with the largest distance between nitrogens (11.9 Å) showed the largest shift of the Soret band to ~421 nm. This data confirms that the degree to which the porphyrin Soret band red shifts depends on the distance between the binding sites.

III.6: Conclusions

The ECCD analysis of the 1,n-glycols with C5-Zn-TPFP-Tweezer lead to the synthesis of a series of Zn-TPFP-Tweezers with different linker lengths in order optimize the TPFP tweezer. The C3-Zn-TPFP-Tweezer with the shortest linker, was found to be the only consistent and reliable tweezer for this class of compounds. To explain the large ECCD amplitudes and the small shifts of the porphyrin Soret band in UV-Vis, a new binding model was proposed. The side-on binding mode accounted for the large ECCD amplitudes because the porphyrins remain in close proximity when bound to the glycol. Also, the porphyrins will rotate away from one another to accommodate the longer glycols. The combination of the close porphyrins and increasing angle lead to intense ECCD amplitudes. The close proximity of the porphyrins would also explain the small changes in the porphyrin Soret band shift in UV-Vis analysis. Finally, to confirm that the Soret band shifts are an indication of binding mode, a series of bispyridine compounds were synthesized. The location of the nitrogen lone pairs are held fixed in space therefore, the operational binding mode was controlled.

III.7: Experimental Procedures

III.7.1: General Procedures

Where it is stated that dry CH_2Cl_2 or dry toluene was used, the solvent was distilled over CaH_2 . Dry THF and diethyl ether were obtained by distillation from sodium benzophenone ketyl. All other reagents, unless indicated otherwise, were purchased from commercial sources.

Thin layer chromatography was performed on Merck aluminum sheets coated with silica gel (0.2mm thickness). Potassium permanganate, anisaldehyde, polymolybdic acid and UV were used for visualization. Silica chromatography was performed using Dynamic Adsorbents Inc Flash Silica Gel 32-634.

^1H NMR was recorded with Varian Inova 300 or 500 MHz instruments in CDCl_3 . The reported ^1H NMR chemical shifts are relative to the CDCl_3 line (7.24 ppm) and the ^{13}C NMR chemical shifts are relative to the central CDCl_3 line (77.0 ppm). ^{19}F NMR was recorded on the 300 MHz instrument. Mass spectra were recorded using Mass Spectrometry Laboratory using micromass VG-70 mass spectrometer. UV/Vis spectra were recorded on a Perkin-Elmer Lambda 40 spectrophotometer. The CD spectra were recorded on a Jasco J-810 spectropolarimeter equipped with a Neslab 111 temperature controller.

III.7.2: General Procedure for ECCD Measurement

To hexanes (1 mL) in a 1.0 cm cell, 2 μL of a 1 mM stock solution of zinc porphyrin tweezer (C5-Zn-TPFP-Tz) in anhydrous CH_2Cl_2 was added to provide a 2 μM tweezer solution. The background spectrum was recorded from 380 nm to 450 nm at a scan rate of 50 nm/min at

the specified temperature. Each chiral guest molecule was dissolved in anhydrous CH_2Cl_2 to afford a 1 mM solution then 0.2 to 100 μL of this solution was added to the cell with the tweezer solution affording the host-guest complex. For substrates that required high concentration of guest, a 10 mM solution in anhydrous CH_2Cl_2 was prepared then 1 to 100 μL of this solution was added to the cell with the tweezer solution. The ECCD spectra was immediately recorded following addition of the guest solution (minimum of 4 accumulations). The resultant ECCD spectra, which is reported in millidegrees, was normalized to the tweezer concentration to obtain molecular CD (Mol CD).

III.7.3: General Procedure for UV-Vis Measurement, Job's Plot Analysis, and Binding Constant Determination

To hexanes (1 mL) in a 1.0 cm cell, 1 μL of a 1 mM stock solution of zinc porphyrin tweezer (C5-Zn-TPFP-Tz) in anhydrous CH_2Cl_2 was added to provide a 1 μM tweezer solution. The background spectrum was recorded from 600 nm to 350 nm at a scan rate of 240 nm/min at room temperature. Each chiral guest molecule was dissolved in anhydrous CH_2Cl_2 to afford a 1 mM solution then 0.2 to 100 μL of this solution was added to the cell with the tweezer solution affording the host-guest complex. For substrates that required high concentration of guest, a 10 mM solution in anhydrous CH_2Cl_2 was prepared then 1 to 100 μL of this solution was added to the cell with the tweezer solution. The UV-Vis spectrum was collected immediately after addition of the guest solution.

The UV-Vis measurements were manipulated for the purpose of determining the complex stoichiometry by Job's plot analysis. First, the molar fraction of tweezer in the solution

was first determined by dividing the moles of tweezer by the total number of moles (moles of tweezer and moles of guest molecule) present in solution. Second, the change in absorbance with each addition of guest molecule was determined. The molar fraction of tweezer and the change of absorbance were multiplied together. The Job's plot was generated by plotting molar fraction tweezer versus molar fraction tweezer multiplied by change in absorbance in Excel. A parabolic curve is generated and the apex of the parabola provides the molar fraction of tweezer in the host-guest complex. A 1:1 complex is formed when the apex falls at a molar fraction of 0.5.

The UV-Vis measurements were manipulated for the purpose of determining the the binding affinity of the guest molecule for the tweezer. The concentration of the guest molecule was determined based on the equivalents of the guest added to the tweezer solution. Also, the change of absorbance for each addition of the guest was determined. Using, KaleidaGraph a plot of the concentration of guest versus the change in absorbance was generated and a line of best fit was calculated based on the following equation:

$$F = F_0 - \frac{1 + (P_T + R_T)K_a - \sqrt{(P_T - R_T)^2 K_a^2 + 2(P_T + R_T)K_a + 1}}{2(P_T K_a)} (F_0 - F_\infty)$$

F = absorbance of the tweezer at a given concentration of guest.

F₀ = absorbance of the tweezer without guest.

F_∞ = absorbance of the tweezer at saturation with the guest.

P_T = concentration of the tweezer.

R_T = concentration of the guest molecule.

K_a = binding constant.

ECCD Spectra for C3-Zn-TPFP-Tz and C5-Zn-TPFP-Tz were recorded by Dr. Xiaoyong Li. The spectra were reported in his thesis.

III.7.4: Synthesis and Characterization Data for Substrates

5-(4-methylcarboxylphenyl)-10,15,20-tri(pentafluorophenyl)porphyrin (**III.1**):

Pentafluorobenzaldehyde (2.5 g, 12.8 mmol, 3 equiv) 4-formyl methylbenzoate (0.70 g, 4.3 mmol, 1 equiv), and pyrrole (1.19 mL, 1.15 g, 17.2 mmol, 4 equiv) were dissolved in CH_2Cl_2 (1.72 L) in a 3 liter, 3 neck flask covered in aluminum foil. The solution was stirred under N_2 for 15 minutes then $\text{BF}_3 \cdot \text{OEt}_2$ (0.43 mL, 3.44 mmol, 0.8 equiv) was added. The solution was stirred for 2 hours at room temperature. *p*-Chloranil (8.35 g, 34.4 mmol, 8 equiv) was added to the dark solution. Stirring was continued for 1.5 hours then the solvent was removed under reduced pressure. The residue was purified using silica chromatography (50% CH_2Cl_2 /hexane). The solvent was removed under vacuum and the residue was redissolved in CH_2Cl_2 (400 mL). The solution was added to a 2 liter separatory funnel then was washed with NaOH (0.5 M, 200 mL, 3 xs) to remove the excess *p*-Chloranil. The organic layer was dried with Na_2SO_4 and the solvent was removed under vacuum. The resulting residue was purified with silica chromatography (20-50% CH_2Cl_2 /hexane) to afford **III.1** (900 mg, 22%) as a purple solid.

(**III.1**): ^1H NMR (CDCl_3 , 300 MHz): δ 8.91-8.82 (8H, m), 8.46 (2H, d, $J = 8.4$ Hz), 8.29 (2H, d, $J = 8.4$ Hz), 4.12 (3H, s), -2.87 (2H, br s)

Melting Point: decomposition 250 °C.

Matches literature.⁸

5-(4-carboxylphenyl)-10,15,20-tri(pentafluorophenyl)porphyrin (**III.2**): 5-(4-methylcarboxylphenyl)-10,15,20-tri(pentafluorophenyl)porphyrin (**III.1**, 640 mg, 0.68 mmol) was added to NaOH (2 M, 60 mL) and THF (60 mL) in a 500 mL round bottom flask equipped with a reflux condenser. The mixture was stirred and refluxed for 10 hours. The heating mantle was removed and solution was cooled to room temperature. The THF was removed under reduced pressure. The resulting solution and CH₂Cl₂ (600 mL) were added a 2 liter separatory funnel and HCl (3 M) was added until a green color was observed. The organic layer was separated and washed with water (300 mL, 4xs) until a purple-red color persisted. The organic layer was dried with Na₂SO₄ and concentrated to give **III.2** (625 mg, 99%) as a purple solid.

(**III.2**): ¹H NMR (CDCl₃, 300 MHz): δ 8.94-8.83 (8H, m), 8.57 (2H, d, *J* = 8.4 Hz), 8.36 (2H, d, *J* = 8.1 Hz), -2.86 (2H, br s)

Melting Point: decomposition 280 °C.

Matches literature.⁸

Synthesis of Monolinkers (**III.3-III.7**): In a flame dried round bottom flask, 5-(4-carboxylphenyl)-10,15,20-tri(pentafluorophenyl)porphyrin (1 equiv), 1,(*n*+3) terminal diol (1.3 equiv), DMAP (1.3 equiv) and EDC (1.3 equiv) were dissolved in dry CH₂Cl₂ (4:1 CH₂Cl₂:THF for **III.5** and **III.7**) to give a 0.04 M solution of the porphyrin. The reaction was stirred under N₂ for 24 hours at room temperature followed by concentration under vacuum. The crude product was purified using silica chromatography (50%-100% CH₂Cl₂/hexane) to afford **III.3** (57 mg,

36%), **III.4** (57 mg, 52%), **III.5** (66 mg, 59%), **III.6** (13 mg, 49%) and **III.7** (81 mg, 47%) as purple solids.

(III.3): ^1H NMR (CDCl_3 , 300 MHz): δ 8.91 - 8.81 (8H, m), 8.45 (2H, d, J = 8.4 Hz), 8.28 (2H, d, J = 8.7 Hz), 4.56 (2H, t, J = 6.3 Hz), 3.82 (2H, m), 2.07 - 1.98 (2H, m), 1.91 - 1.81 (2H, m), -2.88 (2H, br s)

Melting Point: 175 - 183 °C.

HRMS: $[\text{C}_{49}\text{H}_{24}\text{F}_{15}\text{N}_4\text{O}_3]^+$ observed 1001.1724 m/z calculated 1001.1609 m/z

(III.4): ^1H NMR (CDCl_3 , 300 MHz): δ 8.92 - 8.82 (8H, m), 8.46 (2H, d, J = 8.1 Hz), 8.29 (2H, d, J = 8.1 Hz), 4.52 (2H, t, J = 6.6 Hz), 3.70 (2H, t, J = 6.3 Hz), 1.94 (2H, quintet, J = 7.5, 14.1 Hz), 1.72 - 1.50 (8H, m), -2.87 (2H, br s)

HRMS: $[\text{C}_{50}\text{H}_{26}\text{F}_{15}\text{N}_4\text{O}_3]^+$ observed 1029.1259 m/z calculated 1029.1922 m/z

Melting Point: 172 - 179 °C.

(III.5): ^1H NMR (CDCl_3 , 300 MHz): δ 8.92 - 8.81 (8H, m), 8.46 (2H, d, J = 8.1 Hz), 8.29 (2H, d, J = 8.4 Hz), 4.51 (2H, t, J = 6.9 Hz), 3.68 (2H, t, J = 6.3 Hz), 1.92 (2H, quintet, J = 7.8, 14.4 Hz), 1.63 - 1.46 (10H, m), -2.88 (2H, br s)

HRMS: $[\text{C}_{51}\text{H}_{28}\text{F}_{15}\text{N}_4\text{O}_3]^+$ observed 1043.2078 m/z calculated 1043.2078 m/z

Melting Point: 169 - 174 °C.

(III.6): ^1H NMR (CDCl_3 , 500 MHz): δ 8.90 - 8.87 (6H, m), 8.81 (2H, d, J = 5.0 Hz), 8.45 (2H, m), 8.28 (2H, m), 4.51 (2H, t, J = 6.5 Hz), 3.66 (2H, d, J = 7.0 Hz), 1.91 (2H, pentet, J = 7.0 Hz), 1.61 - 1.40 (10H, m), -2.88 (2H, br. s).

HRMS: $[\text{C}_{52}\text{H}_{30}\text{F}_{15}\text{N}_4\text{O}_3]^+$ observed 1057.2467 m/z calculated 1057.2235 m/z

Melting Point: 152 - 158 °C.

(III.7): ^1H NMR (CDCl_3 , 300 MHz): δ 8.91 - 8.81 (8H, m), 8.45 (2H, d, J = 8.4 Hz), 8.28 (2H, d, J = 8.7 Hz), 4.50 (2H, t, J = 6.6 Hz), 3.64 (2H, t, J = 6.3 Hz), 1.91 (2H, quintet, J = 6.6, 13.5 Hz), 1.91 - 1.81 (2H, m), 1.58 - 1.23 (10H, m), -2.88 (2H, br s)

HRMS: $[\text{C}_{53}\text{H}_{32}\text{F}_{15}\text{N}_4\text{O}_3]^+$ observed 1071.2101 m/z calculated 1071.2391 m/z

Melting Point: 139 - 143 $^\circ\text{C}$.

Synthesis of Tweezers **(III.8-III.12)**: 5-(4-carboxylphenyl)-10,15,20-tri(pentafluorophenyl) porphyrin (1.3 equiv), the appropriate monolinker **(III.3-III.7)**, 1 equiv), DMAP (1.3 equiv) and EDC (1.3 equiv) were dissolved in dry CH_2Cl_2 to make a 0.005 M solution of the monolinker in a flame dried round bottom flask. The solution was stirred under N_2 for 24 hours at room temperature followed by concentration under vacuum. The residue was purified using silica chromatography (50% CH_2Cl_2 /hexane) to afford **III.8** (43 mg, 45%), **III.9** (9 mg, 24%), **III.10** (14 mg, 30%), **III.11** (3 mg, 21%) and **III.12** (28 mg, 28%) as purple solids.

(III.8): ^1H NMR (CDCl_3 , 300 MHz): δ 8.91 - 8.79 (16H, m), 8.52 (4H, d, J = 8.4 Hz), 8.31 (4H, d, J = 8.7 Hz), 4.70 (4H, br s), 2.24 (4H, br s), -2.89 (4H, bs).

HRMS: $[\text{C}_{94}\text{H}_{37}\text{F}_{30}\text{N}_8\text{O}_4]^+$ observed 1911.2237 m/z calculated 1911.2459 m/z

Melting Point: 202 - 209 $^\circ\text{C}$.

(III.9): ^1H NMR (CDCl_3 , 300 MHz): δ 8.91 - 8.79 (16H, m), 8.48 (4H, d, J = 8.4 Hz), 8.29 (4H, d, J = 8.7 Hz), 4.58 (4H, t, J = 6.6 Hz), 2.04 (4H, m), 1.72 (4H, m), -2.89 (4H, bs)

HRMS: $[\text{C}_{95}\text{H}_{39}\text{F}_{30}\text{N}_8\text{O}_4]^+$ observed 1071.2101 m/z calculated 1071.2391 m/z

Melting Point: 152 - 163 $^\circ\text{C}$.

(III.10): ^1H NMR (CDCl_3 , 300 MHz): δ 8.91 - 8.79 (16H, m), 8.48 (4H, d, J = 8.4 Hz), 8.29 (4H, d, J = 8.7 Hz), 4.58 (4H, t, J = 6.6 Hz), 2.00 (4H, m), 1.66 (6H, m), -2.89 (4H, bs)

HRMS: $[\text{C}_{96}\text{H}_{41}\text{F}_{30}\text{N}_8\text{O}_4]^+$ observed 1939.3142 m/z calculated 1939.2772 m/z

Melting Point: 194 - 203 $^\circ\text{C}$.

(III.11): ^1H NMR (CDCl_3 , 500 MHz): δ 8.92 - 8.90 (12H, m), 8.82 (4H, d, J = 4.0 Hz), 8.48 (4H, m), 8.31 (4H, m), 4.57 (4H, t, J = 6.5 Hz), 1.98 (4H, pentet, J = 7.0 Hz), 1.68 - 1.58 (8H, m), -2.86 (4H, br. s).

HRMS: $[\text{C}_{97}\text{H}_{43}\text{F}_{30}\text{N}_8\text{O}_4]^+$ observed 1967.2894 m/z calculated 1967.3085 m/z

Melting Point: 187 - 191 $^\circ\text{C}$.

(III.12): ^1H NMR (CDCl_3 , 300 MHz): δ 8.91 - 8.80 (16H, m), 8.46 (4H, d, J = 8.4 Hz), 8.28 (4H, d, J = 8.7 Hz), 4.55 (4H, t, J = 6.6 Hz), 1.95 (4H, quintet, J = 7.8, 14.7 Hz), 1.62 - 1.24 (10H, m), -2.88 (4H, bs).

HRMS: $[\text{C}_{98}\text{H}_{45}\text{F}_{30}\text{N}_8\text{O}_4]^+$ observed 1981.3329 m/z calculated 1981.3241 m/z

Melting Point: 242 - 250 $^\circ\text{C}$.

Synthesis of Zincated Tweezers (III.13-III.17): The appropriate tweezer (III.8-III.12) and an excess of $\text{Zn}(\text{OAc})_2$ dihydrate were dissolved in dry CH_2Cl_2 in a flame dried round bottom flask, shielded from light. The solution was stirred under N_2 for 48 hours at room temperature followed by concentration under vacuum. The resulting residue was purified using silica chromatography (50%-100% CH_2Cl_2 /hexane) to afford III.13 (14.3 mg, 21%), III.14 (6.5 mg, 74%), III.15 (9.2 mg, 63%), III.16 (3 mg, 50%) and III.17 (13.7 mg, 20%) as pink solids.

(III.13): ^1H NMR (CDCl_3 , 300 MHz): δ 8.93 - 8.86 (16H, m), 8.23 (4H, d, J = 8.4 Hz), 8.04 (4H, d, J = 8.1 Hz), 3.79 (4H, br s), 2.06 (4H, br s)

HRMS: $[\text{C}_{94}\text{H}_{33}\text{F}_{30}\text{N}_8\text{O}_4\text{Zn}_2]^+$ observed 2035.0910 m/z calculated 2035.0729 m/z

Melting Point: 236 - 243 $^\circ\text{C}$.

(III.14): ^1H NMR (CDCl_3 , 300 MHz): δ 8.98 - 8.88 (16H, m), 8.32 (4H, d, J = 8.4 Hz), 8.25 (4H, d, J = 8.4 Hz), 4.39 (4H, t, J = 6.6 Hz), 1.86 (4H, m), 1.56 (6H, m)

HRMS: $[\text{C}_{95}\text{H}_{35}\text{F}_{30}\text{N}_8\text{O}_4\text{Zn}_2]^+$ observed 1981.2762 m/z calculated 1981.3241 m/z

Melting Point: 272 - 276 $^\circ\text{C}$.

(III.15): ^1H NMR (CDCl_3 , 300 MHz): δ 8.96 - 8.87 (16H, m), 8.23 (4H, s), 4.27 (4H, t, J = 6.6 Hz), 1.93 (4H, m), 1.68 (4H, m)

HRMS: $[\text{C}_{96}\text{H}_{37}\text{F}_{30}\text{N}_8\text{O}_4\text{Zn}_2]^+$ observed 2063.0985 m/z calculated 2063.1042 m/z

Melting Point: 259 - 264 $^\circ\text{C}$.

(III.16): ^1H NMR (CDCl_3 , 300 MHz): δ 8.97 - 8.93 (12H, m), 8.89 - 8.87 (4H, m), 8.35 (4H, m), 8.25 (4H, m), 4.17 (4H, t, J = 6.6 Hz), 1.91 (4H, pentet, J = 6.9 Hz), 1.68 - 1.54 (8H, m).

HRMS: $[\text{C}_{97}\text{H}_{39}\text{F}_{30}\text{N}_8\text{O}_4\text{Zn}_2]^+$ observed 2077.1203 m/z calculated 2077.1198 m/z

Melting Point: 245 - 249 $^\circ\text{C}$.

(III.17): ^1H NMR (CDCl_3 , 300 MHz): δ 9.03 - 8.93 (16H, m), 8.25 (4H, d, J = 8.1 Hz), 8.15 (4H, d, J = 7.8 Hz), 4.16 (4H, t, J = 6.3 Hz), 1.81 (4H, t, J = 6.6 Hz), 1.57 - 1.29 (10H, m)

HRMS: $[\text{C}_{98}\text{H}_{41}\text{F}_{30}\text{N}_8\text{O}_4\text{Zn}_2]^+$ observed 2105.1325 m/z calculated 2105.1511 m/z

Melting Point: 261 - 269 $^\circ\text{C}$.

3,3'-bipyridine (3,3'-bpy, **III.18**):⁶⁷ Bis(triphenylphosphine) nickel (II) chloride (196 mg, 0.3 mmol, 0.3 equiv) and tetraethylammonium iodide (257 mg, 1 mmol, 1 equiv) were added to THF (2 mL, dry) to a dry 25 mL stirring in round bottom under N₂. Then zinc dust (98.1 mg, 1.5 mmol, 1.5 equiv) was added. After 30 minutes, the reaction mixture was heated to 50 °C then 3-bromopyridine (158 mg, 0.1 mL, 1 mmol, 1 equiv) in THF (5 mL, dry) was added. After 12 hours, the mixture was poured over NH₄OH (2M, 10 mL) then extracted with Et₂O:toluene (1:1, 10 mL, 3 xs). The organic layers were combined and washed with H₂O (20 mL) then NaCl (aq. sat., 20 mL) and dried with Na₂SO₄. The solvent was removed under reduced pressure to provide the crude product. The crude was dissolved in ethyl acetate (20 mL) and it was extracted with HCl (10%, 20 mL, 3 xs). The HCl layers were combined and the water was removed under reduced pressure. To this NaOH (2M, 20 mL) was added and the aqueous layer was extracted with ethyl acetate (20 mL, 3 xs). The organic layers were combined, washed with H₂O (20 mL) then NaCl (aq. sat., 20 mL) and dried with Na₂SO₄. The solvent was removed under reduced pressure to provide the desired product as a off-white solid (15 mg, 19%). Matches literature reported ¹H and ¹³C NMR spectra.

(**III.18**): ¹H NMR (CDCl₃, 500 MHz): δ 8.83 (2H, d, *J* = 1.5 Hz), 8.64 (2H, dd, *J* = 1.0, 5.0 Hz), 7.68 (2H, ddd, *J* = 1.0, 2.5, 8.0 Hz), 7.39 (2H, dd, *J* = 1.0, 8.0 Hz).

¹³C NMR (CDCl₃, 125 MHz): δ 149.4, 148.3, 134.4, 133.5, 123.8.

HRMS: [C₁₀H₉N₂]⁺ observed 157.0582 m/z calculated 157.0766 m/z.

Melting Point: 65 - 67 °C.

Matches literature reported values.

4,4'-bipyridine (4,4'-bipy, **III.19**): ⁶⁸ To 4-bromopyridine hydrochloride (195 mg, 1 mmol, 1 equiv) NaOH (2M, 15 mL) was added. The aqueous layer was extracted with dichloromethane (10 mL, 3 xs). The organic layers were combined, washed with NaCl (aq. sat., 20 mL) and dried with Na₂SO₄. The solvent was removed under reduced pressure to provide the free base 4-bromopyridine. This was used directly without characterization.

Bis(triphenylphosphine) nickel (II) chloride (196 mg, 0.3 mmol, 0.3 equiv) and tetraethylammonium iodide (257 mg, 1 mmol, 1 equiv) were added to THF (2 mL, dry) to a dry 25 mL stirring in round bottom under N₂. Zinc dust (98.1 mg, 1.5 mmol, 1.5 equiv) was then added. After 30 minutes, the reaction mixture was heated to 50 °C then 4-bromopyridine (158 mg, 0.1 mL, 1 mmol, 1 equiv) in THF (5 mL, dry) was added. After 12 hours, the mixture was poured over NH₄OH (2 M, 10 mL) then extracted with Et₂O:toluene (1:1, 10 mL, 3 xs). The organic layers were combined and washed with H₂O (20 mL) then NaCl (aq. sat., 20 mL) and dried with Na₂SO₄. The solvent was removed under reduced pressure to provide the crude product. The crude was dissolved in ethyl acetate (20 mL) and it was extracted with HCl (10%, 20 mL, 3 xs). The HCl layers were combined and the water was removed under reduced pressure. To this NaOH (2 M, 20 mL) was added and the aqueous layer was extracted with ethyl acetate (20 mL, 3 xs). The organic layers were combined, washed with H₂O (20 mL) then NaCl (aq. sat., 20 mL) and dried with Na₂SO₄. The solvent was removed under reduced pressure to provide the desired product as a off-white solid (6 mg, 7%)

(**III.19**): ¹H NMR (CDCl₃, 500 MHz): δ 8.73 (4H, dd, *J* = 2.0, 4.5 Hz), 7.52 (4H, dd, *J* = 1.5, 4.5 Hz).

¹³C NMR (CDCl₃, 125 MHz): δ 150.7, 145.5, 121.4.

HRMS: [C₁₀H₉N₂]⁺ observed 157.0863 m/z calculated 157.0766 m/z.

Melting Point: 110 - 113 °C.

Matches literature reported values.

3-(2-trimethylsilyl)ethynyl pyridine (**III.20**):⁶⁹ In a flame dried 3-neck flask under N₂, 2-bromopyridine (505 mg, 0.3 mL, 3.2 mmol, 1 equiv), tetrakis(triphenylphosphine) palladium (369 mg, 0.32 mmol, 10 mol%) and copper (I) iodide (61 mg, 0.32 mmol, 10 mol%) were added. Diisopropylamine (10 mL) was added and the reaction was heated to 35 °C then (trimethylsilyl) acetylene (350 mg, 0.5 mL, 3.5 mmol, 1.1 equiv) was added dropwise. After 3 hours, the reaction was quenched with NH₄Cl (aq. 5 mL) then extracted with diethyl ether (5 mL, 3 xs). The organic layers were combined, washed with NaHCO₃ (aq. sat. 15 mL) and H₂O (15 mL). The organic layer was passed through a celite plug then the solvent was removed under reduced pressure. The crude was dissolved in dichloromethane and was extracted with HCl (10%, 3 xs, 10 mL). The aqueous layers were combined and the water was removed under vacuum. To this, NaOH (2 M, 15 mL) was added and the aqueous layer was extracted with dichloromethane (10 mL, 3 xs). The organic layers were combined and dried with Na₂SO₄, and the solvent was removed under reduced pressure to provide the product as a brown liquid (196 mg, 35%).

(**III.20**): ¹H NMR (CDCl₃, 500 MHz): 8.64 (1H, s), 8.50 (1H, d, *J* = 5.0 Hz), 7.72 (1H, m), 7.18 (1H, m), 0.24 (9H, s).

HRMS: [C₁₀H₁₄NSi]⁺ observed 176.0782 m/z calculated 176.0896 m/z.

Matches literature reported values.

2-(2-trimethylsilyl)ethynyl pyridine (**III.21**):⁶⁹ In a flame dried 3-neck flask under N₂, 3-bromopyridine (505 mg, 0.3 mL, 3.2 mmol, 1 equiv), tetrakis(triphenylphosphine) palladium (369 mg, 0.32 mmol, 10 mol%) and copper (I) iodide (61 mg, 0.16 mmol, 10 mol%) were added. Diisopropylamine (10 mL) was added and the reaction was heated to 35 °C then (trimethylsilyl)acetylene (350 mg, 0.5 mL, 3.5 mmol, 1.1 equiv) was added dropwise. After 3 hours, the reaction was quenched with NH₄Cl (aq. 5 mL) then extracted with diethyl ether (5 mL, 3 xs). The organic layers were combined, washed with NaHCO₃ (aq. sat. 15 mL) and H₂O (15 mL). The organic layer was passed through a celite plug then the solvent was removed under reduced pressure. The crude was dissolved in dichloromethane and was extracted with HCl (10%, 10 mL, 3 xs). The aqueous layers were combined and the water was removed under vacuum. To this, NaOH (2 M, 15 mL) was added and the aqueous layer was extracted with dichloromethane (10 mL, 3 xs). The organic layers were combined and dried with Na₂SO₄, and the solvent was removed under reduced pressure to provide the product as a brown liquid (235 mg, 42%).

(**III.21**): ¹H NMR (CDCl₃, 500 MHz): 8.56 (1H, m), 7.63 (1H, dt, *J* = 2.0, 8.0 Hz), 7.45 (1H, dt, *J* = 2.0, 7.5 Hz), 7.23 (1H, m), 0.24 (9H, s).

HRMS: [C₁₀H₁₄NSi]⁺ observed 176.1134 m/z calculated 176.0896 m/z.

Matches literature reported values.

4-ethynylpyridine (**III.22**):⁷⁰ In a flame dried 3-neck flask under N₂, 4-bromopyridine (122 mg, 0.63 mmol, 1 equiv), tetrakis(triphenylphosphine) palladium (19 mg, 0.016 mmol, 10 mol%) and copper (I) iodide (3 mg, 0.16 mmol, 10 mol%) were added. Diisopropylamine (2 mL) was added and the reaction was heated to 30 °C then (trimethylsilyl)acetylene (70 mg, 0.1 mL, 0.7 mmol,

1.1 equiv) was added dropwise. After 3 hours, the reaction was quenched with NH_4Cl (aq. 5 mL) and extracted with diethyl ether (5 mL, 3 xs). The organic layers were combined, washed with NaHCO_3 (aq. sat. 15 mL) and H_2O (15 mL). The organic layer was passed through a celite plug and the solvent was removed under reduced pressure. The crude was dissolved in dichloromethane and was extracted with HCl (10%, 10 mL, 3 xs). The aqueous layers were combined and the water was removed under vacuum. To this, NaOH (2 M, 15 mL) was added and the aqueous layer was extracted with dichloromethane (10 mL, 3 xs). The organic layers were combined and dried with Na_2SO_4 , and the solvent was removed under reduced pressure to provide the product as a brown liquid (18.7 mg, 17%).

(III.22): ^1H NMR (CDCl_3 , 500 MHz): δ 8.56 (2H, dd, J = 1.5, 4.0 Hz), 7.32 (2H, dd, J = 2.0, 4.5 Hz), 3.26 (1H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 149.8, 130.3, 126.0, 81.8, 80.9.

Mass Spectrum: $[\text{C}_7\text{H}_6\text{N}]^+$ observed 104.0 m/z calculated 104.1 m/z.

Matches literature reported values.

3-ethynylpyridine (III.23):⁷¹ 3-(2-trimethylsilyl)ethynyl pyridine (100 mg, 0.57 mmol, 1 equiv) was dissolved in methanol (10 mL) in a 50 mL round bottom flask. To this an excess of K_2CO_3 was added and the mixture was stirred at room temperature for 30 minutes. Water (10 mL) was then added to dissolve the salt and the aqueous layer was extracted with dichloromethane (25 mL, 3 xs). The organic layers were combined, washed with NaCl (aq. sat., 25 mL) and dried with Na_2SO_4 . The solvent was removed under reduced pressure. The product was isolated as a brown liquid (56 mg, 98%).

(III.23): ^1H NMR (CDCl_3 , 500 MHz): δ 8.70 (1H, d, J = 1.5 Hz), 8.54 (1H, dd, J = 1.5, 5.0 Hz), 7.68 (1H, dt, J = 1.5, 6.5 Hz), 7.22 (1H, dd, J = 0.5, 8.5 Hz) 3.19 (1H, s).

Mass Spectrum: $[\text{C}_7\text{H}_6\text{N}]^+$ observed 104.1 m/z calculated 104.1 m/z.

Matches literature reported values.

2-ethynylpyridine (III.24):⁷² 2-(2-trimethylsilyl)ethynyl pyridine (100 mg, 0.57 mmol, 1 equiv) was dissolved in methanol (10 mL) in a 50 mL round bottom flask. To this an excess of K_2CO_3 was added and the mixture was stirred at room temperature for 30 minutes. Water (10 mL) was then added to dissolve the salt and the aqueous layer was extracted with dichloromethane (25 mL, 3 xs). The organic layers were combined, washed with NaCl (aq. sat., 25 mL) and dried with Na_2SO_4 . The solvent was removed under reduced pressure. The product was isolated as a brown liquid (55 mg, 93%).

(III.24): ^1H NMR (CDCl_3 , 500 MHz): δ 8.56 (1H, ddd, J = 1.0, 2.0, 5.0 Hz), 7.62 (1H, dt, J = 2.0, 8.0 Hz), 7.44 (1H, dt, J = 1.0, 7.5 Hz), 7.22 (1H, dd, J = 1.0, 5.0 Hz), 3.12 (1H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 150.0, 142.4, 136.1, 127.4, 123.4, 82.7, 77.0.

Mass Spectrum: $[\text{C}_7\text{H}_6\text{N}]^+$ observed 104.1 m/z calculated 104.1 m/z.

Matches literature reported values.

1,2-di(pyridin-3-yl)ethyne (III.25):⁷³ In a flame dried 3-neck flask under N_2 , 2-bromopyridine (18 mg, 0.1 mL, 1.1 mmol, 1 equiv), tetrakis(triphenylphosphine) palladium (115 mg, 0.1 mmol, 10 mol%) and copper (I) iodide (19 mg, 0.1 mmol, 10 mol%) were added. Diisopropylamine (3 mL) was added and the reaction was heated to 35 °C then 3-ethynylpyridine (III.23, 10 mg, 1.0

mmol, 1.1 equiv) in dichloromethane (0.5 mL) was added dropwise. After 3 hours, the reaction was quenched with NH_4Cl (aq. 5 mL) then extracted with diethyl ether (5 mL, 3 xs). The organic layers were combined, washed with NaHCO_3 (aq. sat. 15 mL) and H_2O (15 mL). The organic layer was passed through a celite plug then the solvent was removed under reduced pressure. The crude was dissolved in dichloromethane and was extracted with HCl (10%, 10 mL, 3 xs). The aqueous layers were combined and the water was removed under vacuum. To this, NaOH (2 M, 15 mL) was added then the aqueous layer was extracted with dichloromethane (10 mL, 3 xs). The organic layers were combined and dried with Na_2SO_4 then the solvent was removed under reduced pressure to provide the product as a yellow solid (23 mg, 12%).

(III.25): ^1H NMR (CDCl_3 , 500 MHz): δ 8.78 (2H, d, $J = 3.0$ Hz), 8.59 (2H, d, $J = 7.5$ Hz), 7.84 (2H, dt, $J = 8.0, 2.0$ Hz), 7.35 - 7.28 (2H, m).

^{13}C NMR (CDCl_3 , 125 MHz): δ 152.1, 148.8, 138.4, 123.0, 119.5, 89.5

Mass Spectrum: $[\text{C}_{12}\text{H}_9\text{N}_2]^+$ observed 181.1 m/z calculated 181.1 m/z.

Melting Point: 55 - 59 °C.

Matches reported literature values.

1,2-di(pyridin-2-yl)ethyne (III.26):⁷⁴ In a flame dried 3-neck flask under N_2 , 2-bromopyridine (18 mg, 0.1 mL, 1.1 mmol, 1 equiv), tetrakis(triphenylphosphine) palladium (115 mg, 0.1 mmol, 10 mol%) and copper (I) iodide (19 mg, 0.1 mmol, 10 mol%) were added. Diisopropylamine (3 mL) was added and the reaction was heated to 30 °C then 2-ethynylpyridine (III.24, 10 mg, 1.0 mmol, 1.1 equiv) in dichloromethane (1.5 mL) was added dropwise. After 3 hours, the reaction was quenched with NH_4Cl (aq. 5 mL) and extracted with diethyl ether (5 mL, 3 xs). The organic

layers were combined, washed with NaHCO₃ (aq. sat. 15 mL) and H₂O (15 mL). The organic layer was passed through a celite plug and the solvent was removed under reduced pressure. The crude was dissolved in dichloromethane and was extracted with HCl (10%, 10 mL, 3 xs). The aqueous layers were combined and the water was removed under vacuum. To this, NaOH (2 M, 15 mL) was added and the aqueous layer was extracted with dichloromethane (10 mL, 3 xs). The organic layers were combined and dried with Na₂SO₄ and the solvent was removed under reduced pressure to provide the product as a yellow solid (10 mg, 5%).

(III.26): ¹H NMR (CDCl₃, 500 MHz): δ 8.64 (2H, d, *J* = 4.5 Hz), 7.73 (2H, t, *J* = 7.5 Hz), 7.63 (2H, d, *J* = 8.0 Hz), 7.28 (2H, t, *J* = 7.0 Hz).

¹³C NMR (CDCl₃, 125 MHz): δ 150.4, 143.0, 136.4, 128.1, 123.6, 88.2

Mass Spectrum: [C₁₂H₉N₂]⁺ observed 181.0 m/z calculated 181.1 m/z.

Melting Point: 60 - 65 °C.

Matches literature values.

1,2-di(pyridin-4-yl)ethyne (III.27):⁷⁵ In a flame dried 3-neck flask under N₂, 4-bromopyridine hydrochloride (18 mg, 0.09 mmol, 1 equiv), tetrakis(triphenylphosphine) palladium (10.5 mg, 0.009 mmol, 10 mol%) and copper (I) iodide (2 mg, 0.009 mmol, 10 mol%) were added. Diisopropylamine (3 mL) and dichloromethane (2 mL, dry) were added and the reaction was heated to 30 °C then 4-ethynyl pyridine (III.22, 10 mg, 0.1 mmol, 1.1 equiv) in dichloromethane (0.5 mL) was added dropwise. After 3 hours, the reaction was quenched with NH₄Cl (aq. 5 mL) and extracted with diethyl ether (5 mL, 3 xs). The organic layers were combined, washed with NaHCO₃ (aq. sat. 15 mL) and H₂O (15 mL). The organic layer was passed through a celite plug

and the solvent was removed under reduced pressure. The crude was dissolved in dichloromethane and was extracted with HCl (10%, 10 mL, 3 xs). The aqueous layers were combined and the water was removed under vacuum. To this, NaOH (2 M, 15 mL) was added and the aqueous layer was extracted with dichloromethane (10 mL, 3 xs). The organic layers were combined and dried with Na₂SO₄, and the solvent was removed under reduced pressure to provide the product as a yellow solid (14 mg, 9%).

(III.27): ¹H NMR (CDCl₃, 500 MHz): δ 8.62 (4H, d, *J* = 6.0 Hz), 7.36 (4H, dd, *J* = 1.5, 4.0 Hz).

¹³C NMR (CDCl₃, 125 MHz): δ 149.9, 129.4, 126.0, 80.2.

Mass Spectrum: [C₁₂H₉N₂]⁺ observed 181.1 m/z calculated 181.1 m/z.

Melting Point: 160 - 163 °C.

Matches literature reported values.

1,4-bis(pyridin-3-yl)buta-1,3-diyne (III.28):⁷⁶ 3-ethynylpyridine (III.23, 10 mg, 0.1 mmol, 1 equiv), copper (II) acetate hydrate (168 mg, 0.84 mmol, 8.4 equiv) and pyridine (12 mL) were added to a 25 mL flask under O₂. The mixture was heated to 40 °C for 24 hours. The reaction was cooled to room temperature and diluted with dichloromethane (10 mL). This was washed with H₂O (20 mL) and with NaHCO₃ (aq. sat., 20 mL) until the aqueous layer was clear. The dichloromethane layer was dried with Na₂SO₄, the solvent was removed under reduced pressure to provide the crude product as a yellow solid (6 mg, 33%).

(III.28): ¹H NMR (CDCl₃, 500 MHz): δ 8.75 (2H, d, *J* = 2.0 Hz), 8.58 (2H, dd, *J* = 1.5, 5.0 Hz), 7.80 (2H, dt, *J* = 2.0, 7.5 Hz), 7.28 (2H, dd, *J* = 5.0, 7.5 Hz).

HRMS: [C₁₄H₉N₂]⁺ observed 205.1094 m/z calculated 205.0766 m/z.

Melting Point: 149 - 151 °C.

Matches literature reported values.

1,4-bis(pyridin-2-yl)buta-1,3-diyne (**III.29**):⁷⁷ 2-ethynylpyridine (**III.24**, 10 mg, 0.1 mmol, 1 equiv), copper (II) acetate hydrate (168 mg, 0.84 mmol, 8.4 equiv) and pyridine (12 mL) were added to a 25 mL flask under O₂. The mixture was heated to 40 °C for 24 hours. The reaction was cooled to room temperature and diluted with dichloromethane (10 mL). This was washed with H₂O (20 mL) then with NaHCO₃ (aq. sat., 20 mL) until the aqueous layer was clear. The dichloromethane layer was dried with Na₂SO₄ then the solvent was removed under reduced pressure to provide the crude product as a yellow solid (9 mg, 45%).

(**III.29**): ¹H NMR (CDCl₃, 500 MHz): δ 8.60 (2H, d, *J* = 5.0 Hz), 7.66 (2H, dt, *J* = 1.5, 7.5 Hz), 7.52 (2H, d, *J* = 8.0 Hz), 7.27 (2H, ddd, *J* = 1.0, 5.0, 8.0 Hz).

HRMS: [C₁₄H₉N₂]⁺ observed 205.1047 m/z calculated 205.0766 m/z.

Melting Point: 119 - 122 °C.

Matches literature reported values.

1,4-di(pyridin-4-yl)buta-1,3-diyne (**III.30**):⁷⁵ 4-ethynylpyridine (**III.22**, 10 mg, 0.1 mmol, 1 equiv), copper (II) acetate hydrate (168 mg, 0.84 mmol, 8.4 equiv) and pyridine (12 mL) were added to a 25 mL flask under O₂. The mixture was heated to 40 °C for 24 hours. The reaction was cooled to room temperature and diluted with dichloromethane (10 mL). This was washed with H₂O (20 mL) and with NaHCO₃ (aq. sat., 20 mL) until the aqueous layer was clear. The

dichloromethane layer was dried with Na_2SO_4 , the solvent was removed under reduced pressure to provide the crude product as a yellow solid (4 mg, 21%).

(III.30): ^1H NMR (CDCl_3 , 500 MHz): δ 8.62 (4H, dd, $J = 2.5, 7.5$ Hz), 7.36 (4H, dd, $J = 2.5, 7.0$ Hz).

HRMS: $[\text{C}_{14}\text{H}_9\text{N}_2]^+$ observed 205.1107 m/z calculated 205.0766 m/z.

Melting Point: 199 - 202 $^\circ\text{C}$.

Matches literature reported values.

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Chapter IV

Determination of Absolute Stereochemistry for Chiral Heteroaromatic Alcohols

IV.1: Background

The previous chapters have summarized the research directed toward gaining a better understanding of the underlying factors that govern transfer of chirality from the chiral guest molecule to the achiral porphyrin tweezer. These results will guide further optimization of the porphyrin tweezer toward a general and reliable host system for a variety of guest molecules. In addition to optimization of the porphyrin tweezer, much work has been directed toward developing mnemonics for different classes of chiral molecules with the porphyrin tweezers. The Zn-TPP-tweezer was utilized for the determination of absolute configuration of diamines and derivatized amino alcohols, amino acids,¹ monoamines,^{2,3} monoalcohols⁴ and carboxylic acids.⁵⁻⁷ Determination of absolute configuration of diamines, amino alcohols, vicinal diols⁸, 1,*n*-glycols,⁹ and epoxy alcohols¹⁰ was achieved with the Zn-TPFP tweezers. The drive to expand the substrate scope of ECCD analysis with porphyrin tweezers is attractive for several reasons namely, the non-empirical nature of ECCD, requirement for only micromolar quantities of the chiral guest and minimal acquisition time to obtain an ECCD spectrum (10 minutes). Therefore, if a mnemonic has been previously established for a class of molecules, the configuration of an unknown molecule with a similar scaffold can be quickly and non-empirically determined.

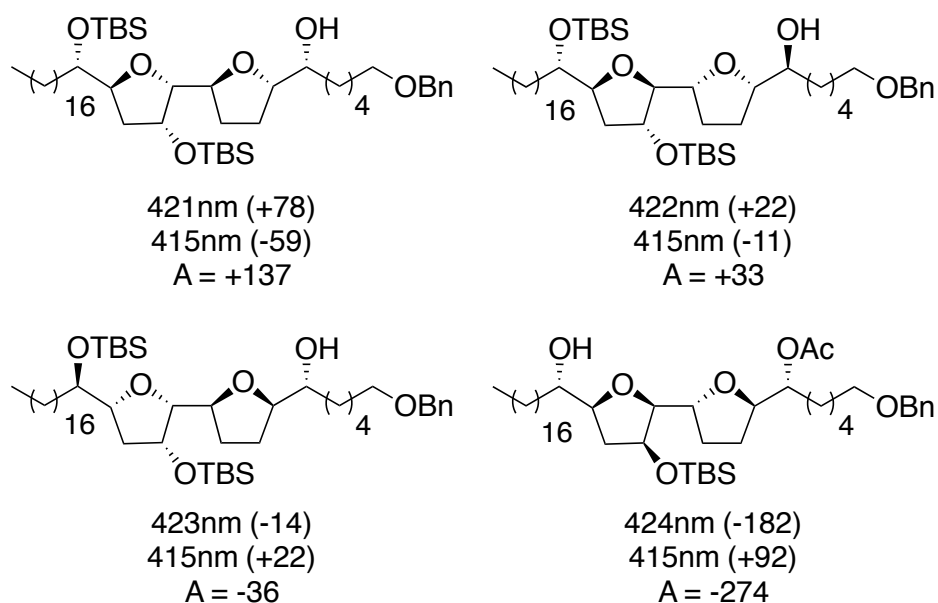
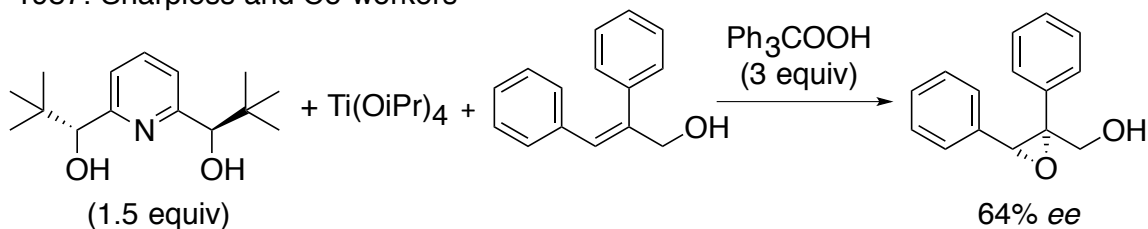


Figure IV.1: ECD analysis of acetogenin type bis-THF molecules with C5-Zn-TPFP-Tweezer.¹¹

With the successful establishment a mnemonic for the epoxy alcohol systems with C5-Zn-TPFP-Tweezer, it was envisioned that the methodology could be extended to chiral molecules where one of the binding sites is part of a heterocycle. For the epoxy alcohols, the tweezer must bind with the ether oxygen of the epoxide therefore, it was hypothesized that the tweezer might also bind with the heteroatom of other saturated heterocycles e.g. tetrahydrofurans (THF), tetrahydropyrans (THP), pyrrolidines, piperidines, etc. As proof of principle, Dr. Xiaoyong Li was able to demonstrate that chiral THF containing molecules will generate an ECD response by the titration of C5-Zn-TPFP-Tweezer with the acetogenin like molecules synthesized by Dr. Jun Yan (Figure IV.1).¹¹

In the same vein, it was hypothesized that determination of absolute configuration of chiral molecules containing a heteroaromatic moiety should also be possible using the porphyrin tweezers. Chiral pyridyl alcohols are of great interest in the fields of asymmetric

1987: Sharpless and Co-workers



1994: Hoshino and Co-workers

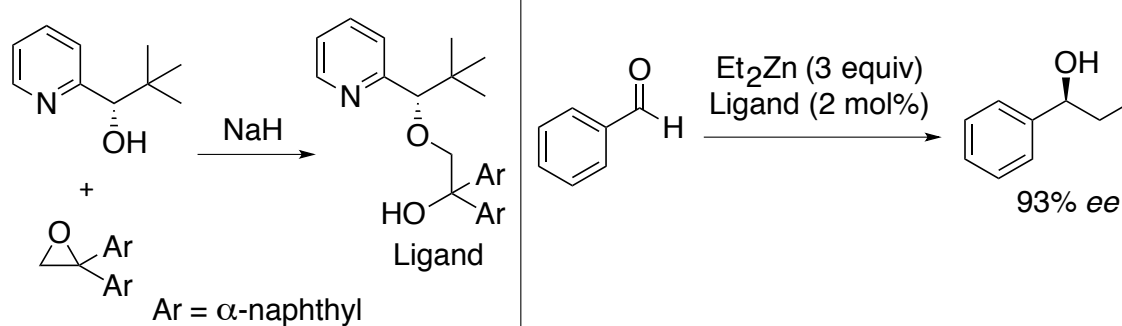
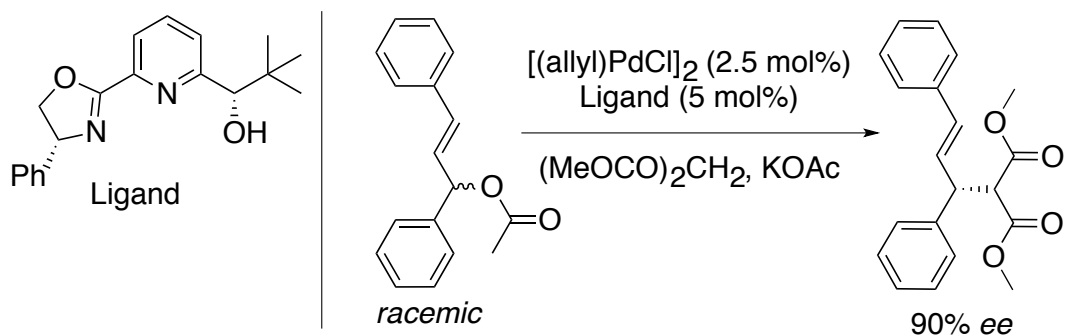


Figure IV.2: Asymmetric synthesis with chiral pyridyl alcohol ligands.^{12,17}

catalysis and pharmaceuticals. Chiral pyridyl alcohols have been utilized as metal ligands in asymmetric synthesis. Sharpless and co-workers have reported the epoxidation of allylic alcohols with titanium (IV) isopropoxide and a 2,6-bis pyridyl methanol (Figure IV.2).¹² These pyridine based ligands have also been employed in cyclopropanation¹³ and addition¹⁴⁻¹⁹ or conjugate addition²⁰⁻²³ of dialkylzinc reagents to aldehydes or α,β -unsaturated ketones. An example by Hoshino and coworkers, Figure IV.2, shows that 2 mol% of the pyridyl alcohol ligand is sufficient for face selective delivery of an ethyl nucleophile from diethyl zinc to benzaldehyde.¹⁷ Moberg and coworkers have demonstrated that derivatization of the 2-pyridyl alcohol with an oxazoline functionality at the C6 position creates an effective ligand for palladium catalyzed allylic alkylations of racemic allyl acetates with dimethyl malonate (Figure IV.3).^{24,25} Conversion of the chiral pyridyl alcohols to chiral phosphites provides an effective ligand for iridium based asymmetric hydrogenation^{26,27} of unactivated alkenes as shown by Pflatz and

1997: Moberg and Co-workers



2004: Pfaltz and Co-workers

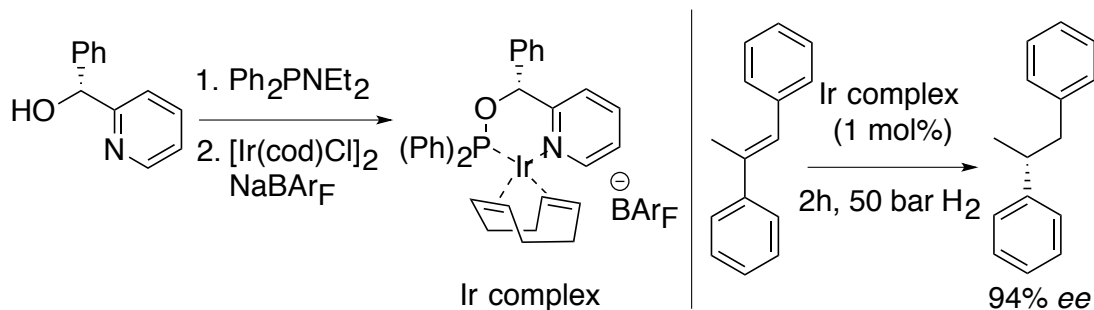


Figure IV.3: Examples of asymmetric synthesis with chiral pyridyl alcohol ligands.^{25,29}

coworkers.^{28,29} These are selected examples of pyridine based ligands for organometallic transformations however, other heteroaromatic molecules such as the pyridine bis-oxazolines (PyBOX) ligands have been employed as metal ligands in a variety of asymmetric synthesis including Michael additions,³⁰⁻³² C-H aminations³³ and allylic substitution³⁴ to name a few. The quinoline alcohol based cinchona alkaloids have also been extensively used in asymmetric organocatalysis particularly in our lab for the development of the asymmetric chlorocyclization reactions.³⁵⁻³⁷

Chiral pyridyl alcohols are of interest to the pharmaceutical industry as well (Figure IV. 4).^{38,39} One of the first reports regarding pyridyl alcohols was in 1970 by Pokorny and co-workers.³⁹ They reported the analgesic activity of racemic α -phenyl-2-pyridyl methanol as well as anticonvulsant activity for a variety of aryl-4-pyridyl ketones. More recently, aryl-2-pyridyl

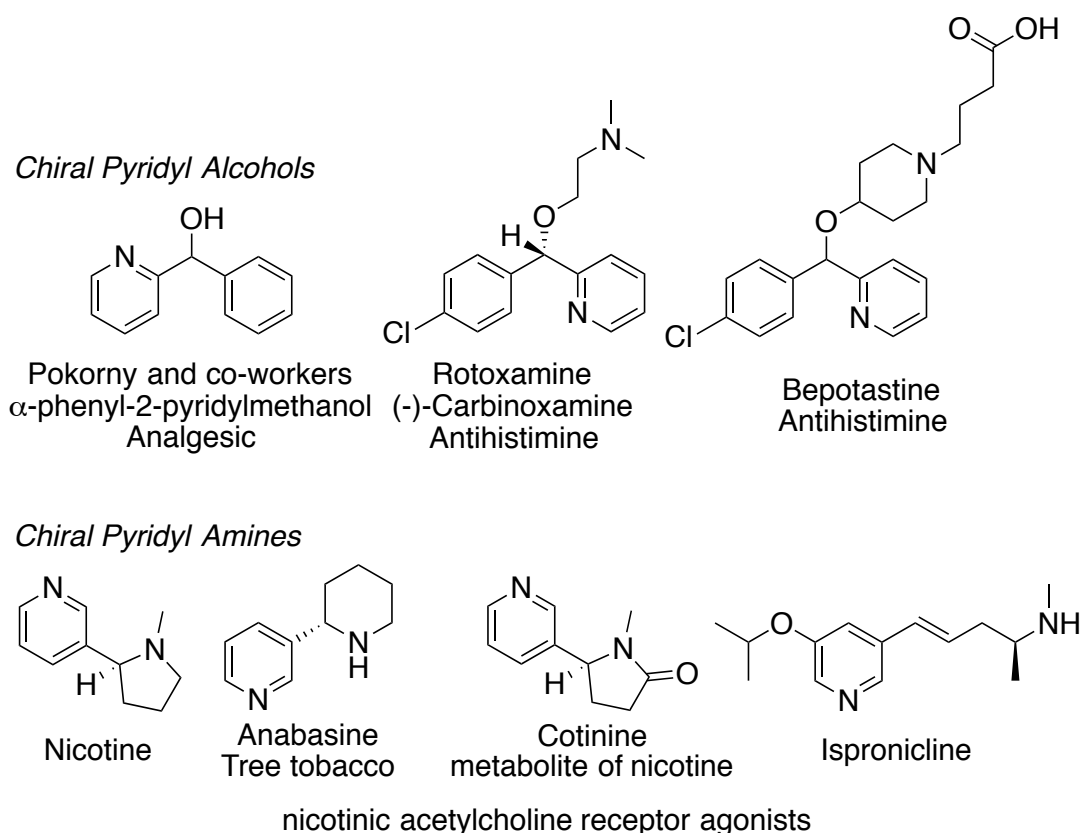


Figure IV.4: Selected biologically active chiral pyridyl alcohols and amines.

alcohols have served as intermediates to some commercially available drugs such as, rotoxamine (carbinoxamine), bepotastine and doxylamine which are known H₁-antagonists (antihistamines). Furthermore, nicotine, anabastine, cotinine, nornicotine and isopronicline are 3-pyridyl amines well known for their roles as nicotinic acetylcholine receptor agonists.

With the development of synthetic methodology, there are an increasing number ways to access chiral heteroaromatic alcohols. These methodologies include resolution of the racemic alcohol,⁴⁰⁻⁴² enzymatic transformation,⁴³⁻⁴⁷ and separation of the racemic alcohol by chiral HPLC.⁴⁸ There also a variety of asymmetric reductions with chiral hydrides,^{49,50} with chiral boranes^{51,52} including Corey-Bakshi-Shibata type reductions,⁵³⁻⁵⁷ by hydrosilylation⁵⁸ and and by hydrogenation (Noyori reductions).^{59,60} Additionally, reactions that allow for the

enantioselective delivery of carbon nucleophiles to pyridyl aldehydes and ketones have been shown to provide access to the chiral alcohols.^{61,62} This scaffold has also been accessed through construction of the pyridine through a cyclotrimerization of a chiral cyanohydrin.⁶³ However, even with the progress in asymmetric synthesis, there has not been as much advancement in the available methodology for determination of absolute stereochemistry of these molecules.

IV.2: Conventional Methods for Determining the Stereochemistry of Chiral Heteroaromatic Alcohols

There are few methods for determining absolute configuration of chiral heteroaromatic alcohols reported. Most commonly chemical correlation,⁶⁴ NMR analysis via Mosher ester derivatization^{65,66} or chiral solvating agents⁶⁷ and circular dichroism^{64,68,69} have been employed.

The use of NMR via Mosher ester analysis to establish absolute configuration was demonstrated in 2008 by Mortreux and co-workers.⁶⁶ The authors accessed the chiral pyridyl alcohols by an asymmetric hydrogenation of the pyridyl ketones using a ruthenium-diamine-diphosphine catalyst and hydrogen gas. The arylpyridyl alcohol obtained from the asymmetric reduction was derivatized by a DCC mediated coupling with (*R*)- α -methoxy-phenylacetic acid, (*R*)-MPA (Figure IV.5 A). It was assumed that the preferred conformation of the MPA ester is such that the methoxy of the MPA moiety lies in the same plane as the hydrogen of the arylpyridyl methanol. Therefore, if the alcohol has an (*S*)-configuration, the (*R,S*) diastereomer, the pyridine interacts with the hydrogen of the MPA and there will be no change in chemical

shift of the pyridine α -proton. Alternatively, for the (*R,R*)-diastereomer of the ester, which is the derivative of the (*R*)-alcohol, the pyridine lies in the shielding zone from the phenyl of the MPA ester. An upfield shift of the pyridine α -proton is expected. The opposite correlation of the pyridine α -proton chemical shift is expected for the (*S*)-MPA esters. Therefore, the

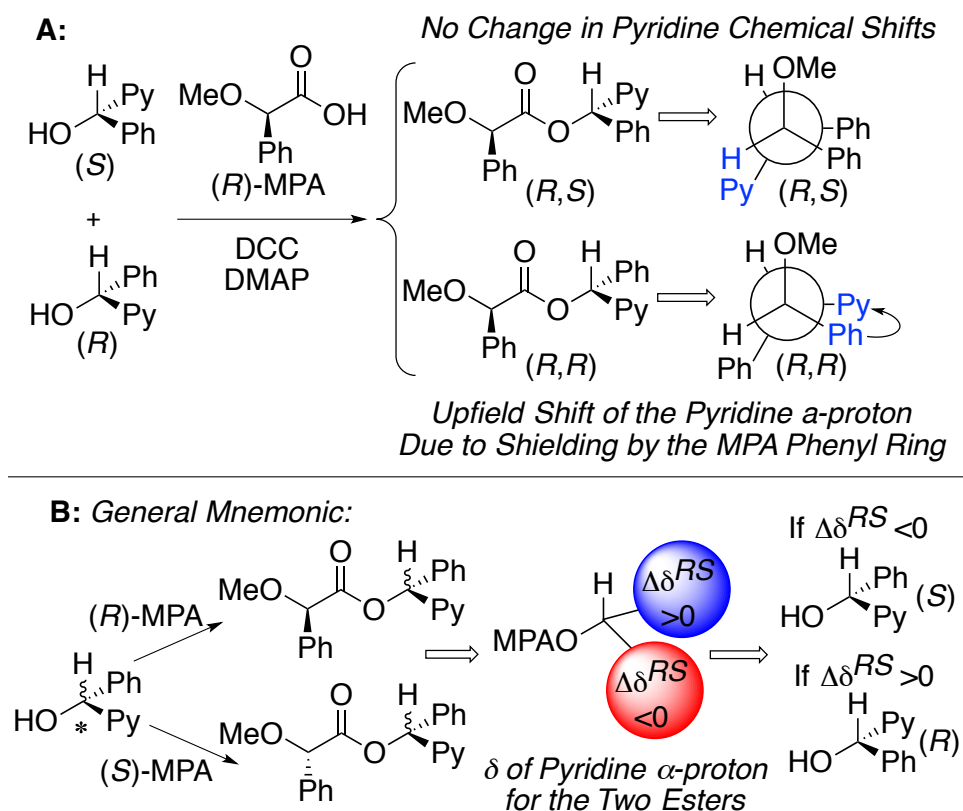


Figure IV.5: Determination of the absolute configuration of chiral pyridyl alcohols by NMR analysis of the (*R*)-MPA esters. There is no change of the pyridine chemical shifts for the (*S*)-arylpyridylmethanol. However, the shielding cone of the phenyl ring of the MPA moiety causes a downfield shift of the (*R*)-arylpyridylmethanol. A general mnemonic was established. Comparison of the pyridine α -proton signals of the diastereomeric Mosher esters can be used to determine the configuration of the alcohol.⁶⁶

configuration of the arylpyridyl alcohol can be determined by the chemical shift of the pyridine α -proton. The pyridine α -proton is typically observed around 8.2 ppm in proton NMR. This signal is often well separated from the NMR signals for the remainder of the molecule thus, only the pyridine α -proton was considered during the analysis. In addition to determining the absolute configuration of the pyridyl alcohol, the NMR of the MPA ester of the chiral alcohol was used to confirm the enantioselectivity of the asymmetric reduction. By integrating the pyridine α -proton signals for the two esters, the enantioselectivity can be determined and compared to the value obtained by HPLC separation.

A general mnemonic could be established for the Mosher ester analysis (Figure IV.5 B). The chiral alcohol was derivatized with both enantiomers of MPA.⁶⁶ The NMR of the diastereomers was then recorded and the chemical shifts of the pyridine α -proton signals were compared. If the pyridine α -proton signal is upfield shifted for the (*R*)-MPA as compared to the (*S*)-MPA ester the alcohol has a (*R*)-configuration. Therefore, if the pyridine α -proton signal is upfield shifted for the (*S*)-MPA as compared to the (*R*)-MPA ester the alcohol has a (*S*)-configuration.

This type of analysis has been shown successful for a limited number of examples. It requires enough of the chiral alcohol to derivatize into both enantiomers of the Mosher ester. Furthermore, the difference in chemical shifts is a result of the ester residing in the assumed conformation. If this conformation is not favored, the mnemonic is no longer applicable.

There is also a circular dichroism based methodology reported for the determination of absolute configuration of various diarylmethanes including arylpyridylmethanols. In the 1990 report from Snatzke and co-workers, several pyridylmethanols were evaluated by circular

dichroism in different solvents.⁶⁹ The authors propose that the $\pi \rightarrow \pi^*$ transition of the pyridine is observed at 270 nm and the $\pi \rightarrow \pi^*$ of the phenyl is observed around 220 nm. These transitions could participate in exciton coupling and the sign of the Cotton effect couplet at 270 and 220 nm could be correlated to the configuration of the arylpyridyl alcohol. To illustrate the author's findings, the ECCD spectra of (*S*)-(+)- α -phenyl-2-pyridylmethanol will be discussed in detail (Figure IV.6). The preferred conformation of (*S*)-(+)- α -phenyl-2-pyridylmethanol was determined by IR analysis to be such that the nitrogen of the pyridine and the hydroxyl group are synperiplanar to one another. This allows for a hydrogen bond between the pyridine and the hydroxyl and rigidifies the molecule. The hydrogen bond forces a fixed conformation of the pyridine and phenyl rings relative to another and for (*S*)-(+)- α -phenyl-2-pyridylmethanol the rings and electronic transition dipole moments (Figure IV.6: bold lines through the rings) would be arranged in a counterclockwise fashion. Therefore, ECCD analysis

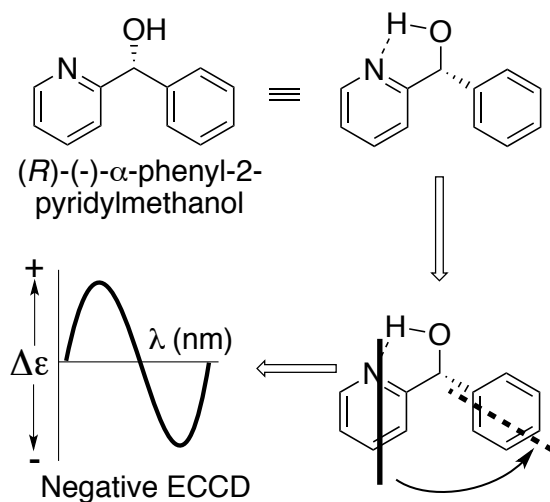


Figure IV.6: ECCD of (*S*)-(+)- α -phenyl-2-pyridylmethanol. Hydrogen bond locks the conformation of the alcohol such that the pyridyl and phenyl groups are arranged in a counterclockwise conformation. Negative ECCD is expected and observed.⁶⁹

should provide a negative ECCD analysis. In non-polar solvents, retention of this hydrogen bond is expected and in cyclohexane a negative ECCD is observed. The first Cotton effect occurs at 261 nm with an amplitude of -7 and the second Cotton effect at 220 nm with an amplitude of +7. The overall ECCD amplitude for (*S*)-(+)- α -phenyl-2-pyridylmethanol in cyclohexane is -14. They note that switching the solvent to methanol destroys the ECCD signal. This is likely due to disruption of the hydrogen bond which would allow the molecule to access any number of ECCD active conformations. The authors successfully analyzed 10 different arylpyridylmethanes in this study.

As with NMR, there are few examples of ECCD analysis of the arylpyridyl methanols. The ECCD methodology also suffers the prerequisite that the pyridylmethanol must have a second aryl substituent for exciton coupling. Therefore, this methodology cannot be extended to α -alkylpyridyl methanols. A general and reliable methodology for the assignment of absolute configuration for not only pyridyl alcohols but a variety of heteroaromatic alcohols is still highly desired.

IV.3: Synthesis of the Chiral Heteroaromatic Alcohols

To determine if chiral heteroaromatic alcohols would bind to a porphyrin tweezer and provide an ECCD signal, the chiral 1-(2-pyridyl)-hexan-1-ol was synthesized by addition of pentylmagnesium bromide to 2-pyridine carboxaldehyde followed by oxidation to the ketone with MnO₂. Subsequent asymmetric reduction under Noyori transfer hydrogenation conditions with RuCl[(*R,R*)-TsDPEN](η^6 -mestylene) in formic acid and triethylamine (2:1)⁵⁹ provided (*R*)-1-(2-pyridyl) hexan-1-ol in 38% yield overall and >99% ee. This chiral alcohol was then subjected

to ECCD conditions with the C3-, C5- and C8-Zn-TPFP-Tweezers (2 μ M, 0 $^{\circ}$ C, hexanes). Since the chiral pyridyl alcohols have similar binding functionalities as amino alcohols, which have been effectively analyzed by the fluorinated, Zn-TPFP-Tweezers,⁸ these tweezers were chosen for analysis of the pyridyl alcohols. Unfortunately, ECCD was not observed with C3- and C5-Zn-TPFP-Tweezers however, a negative ECCD couplet was observed with the C8-Zn-TPFP-Tweezer. The first Cotton effect was observed at 427 nm and the second Cotton effect at 413 nm. An

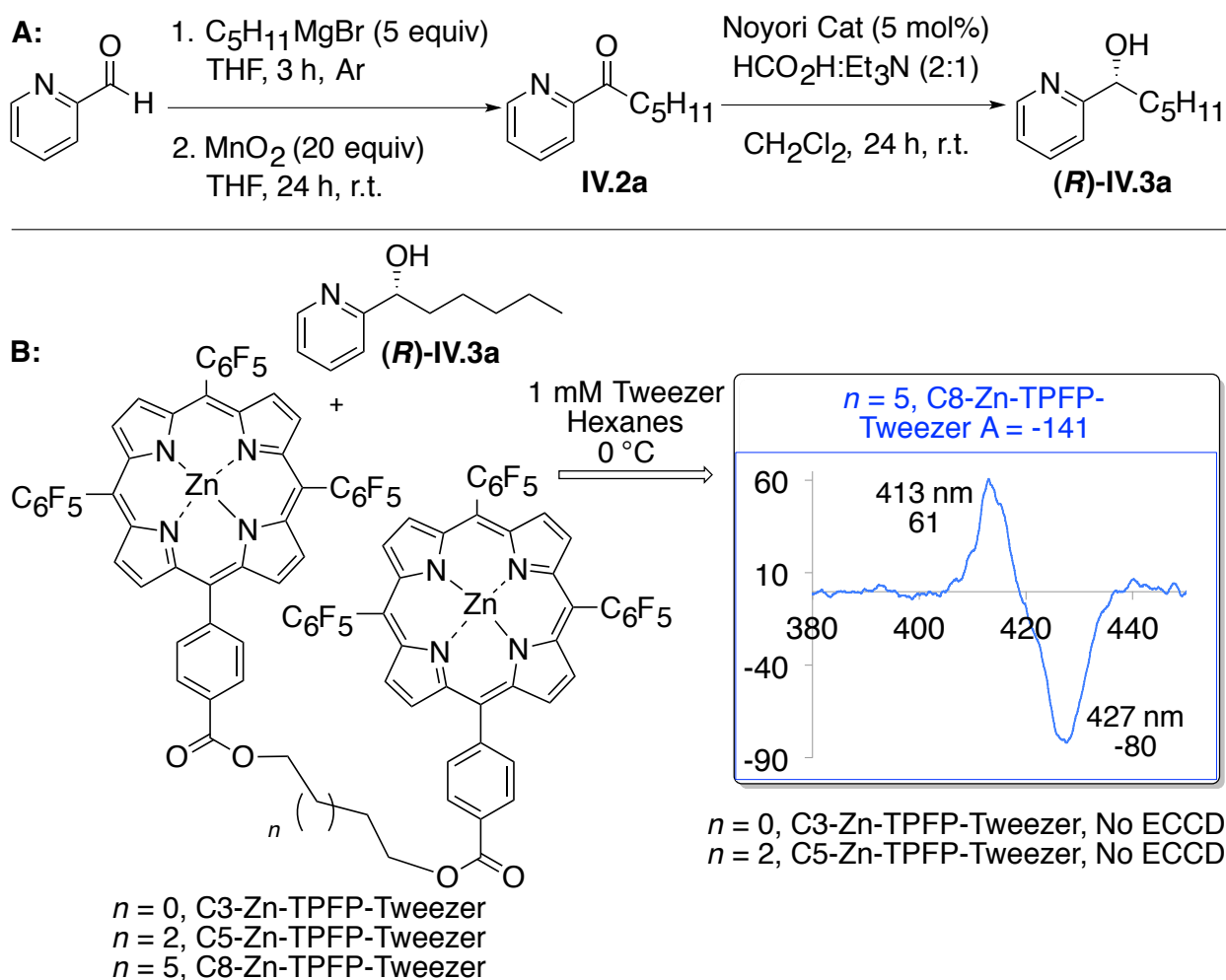


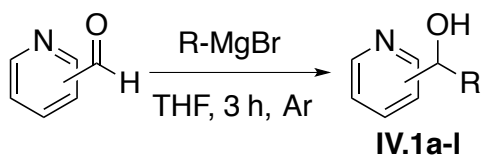
Figure IV.7: ECCD proof of concept with a chiral pyridyl alcohol. **A:** Synthesis of (*R*)-1-(2-pyridyl) hexan-1-ol. **B:** ECCD with C8-Zn-TPFP-Tweezer at 1 μ M tweezer in hexanes at 0 $^{\circ}$ C and 5 equivalents of (*R*)-1-(2-pyridyl) hexan-1-ol.

overall amplitude of -141 was observed with 5 equivalents of the chiral alcohol. The necessity for the C8 linker will be discussed in subsequent sections.

With the proof of concept completed, efforts to establish a general mnemonic for chiral heteroaromatic alcohols was undertaken. A series of chiral substrates with a variety of α -substituents and pyridyl substitution patterns were required. The synthesis of the chiral alcohols were to follow the three step procedure described above for (*R*)-1-(2-pyridyl)-hexan-1-ol. First, either an alkyl or aryl Grignard addition to the appropriate pyridyl aldehyde would provide the racemic alcohols. These alcohols would then be oxidized to the corresponding ketones and subsequent asymmetric reduction of the ketone would generate the chiral pyridyl methanols. These would then be subjected to ECCD analysis.

2-, 3- and 4-pyridyl carboxaldehydes were required for the initial Grignard additions to access the racemic alcohols. 2- and 4-pyridine carboxaldehyde were at hand and 3-pyridine carboxaldehyde was quickly accessed from nicotinic acid through a three step protocol. Esterification of nicotinic acid with methanol under acidic conditions, LAH reduction of the resulting methyl ester and then MnO₂ oxidation provided the 3-pyridyl carboxaldehyde. The Grignard additions to the pyridyl aldehydes proceeded with moderate to high yields in all cases (Table IV.1). For the hexadecylmagnesium bromide, diethyl ether was used instead of THF due to low solubility of 1-bromohexadecane in THF.

With the racemic alcohols in hand, several oxidation conditions were explored as oxidation of 1-(2-pyridyl)-hexan-1-ol (**IV.1a**) with MnO₂ in CH₂Cl₂ gave low yields of the ketone after 48 hours. **IV.1a** was subjected to common conditions such as MnO₂ in THF, Swern, Parikh-Doering, DMP and PCC. Unfortunately, Swern, DMP and PCC failed to provide the desired



Entry	Starting Aldehyde	R	Temp	Product	Yield %
1	2-pyridyl	pentyl	r.t.	IV.1a	54
2	2-pyridyl	methyl	r.t.	IV.1b	67
3	2-pyridyl	isopropyl	reflux	IV.1c	99
4	2-pyridyl	sec-butyl	r.t.	IV.1d	98
5 ^a	2-pyridyl	hexadecyl	r.t.	IV.1e	37
6	3-pyridyl	pentyl	r.t.	IV.1f	17
7	4-pyridyl	pentyl	r.t.	IV.1g	80
8	2-pyridyl	phenyl	reflux	IV.1h	83
9	2-pyridyl	mesityl	reflux	IV.1i	95
10	2-pyridyl	tolyl	reflux	IV.1j	48
11	3-pyridyl	phenyl	reflux	IV.1k	66
12	4-pyridyl	phenyl	reflux	IV.1l	52

Table IV.1: Grignard additions to pyridyl aldehydes to give the racemic pyridyl alcohols

(**IV.1a-IV.1l**). a: diethyl ether was the solvent instead of THF.

ketones but, MnO₂ and Parikh-Doering conditions did provide the ketone, which was then subjected to the Noyori reduction. The ketone from the MnO₂ oxidation was successfully reduced under the Noyori conditions however, when the ketone produce from the Parikh-Doering oxidation was subjected to subsequent Noyori reduction, the ketone was recovered. It is hypothesized that the dimethyl sulfide bi-product of the Parikh-Doering oxidation may have been present with the ketone. The sulfide might bind to the ruthenium catalyst for the Noyori reduction thereby preventing binding and reduction of the ketone as desired. Therefore, MnO₂ was the oxidizing reagent of choice providing access to the pyridyl ketones as reduction of the

ketone from the MnO_2 oxidation was successful. By changing the solvent to from CH_2Cl_2 to THF, higher yields of the ketones was observed.

For each of the Noyori reductions, an (*R*) configuration of the pyridyl alcohol is predicted. Noyori and co-workers have shown through experimental and computational studies that the alcohol generated from a reduction with a ruthenium catalyst bearing an (*R,R*)-diamine (TsDPEN) will provide the aromatic alcohol of (*R*) configuration.⁶⁰ Shown in Figure IV.8 is the structure of the catalyst used and the preferred transition state. The conformation of the five-membered ring containing the diamine and ruthenium is dictated by the stereochemistry of the diamine. The conformation shown is preferred as the phenyl rings of the diamine are equatorial. The oxygen of the ketone hydrogen bonds with the protonated amine and the pyridine ring is thought to enjoy a favorable CH/π interaction with the mesitylene of the ruthenium complex. The hydride is then delivered from the ruthenium to the carbon of the ketone providing the alcohol which in these cases would bear an (*R*) configuration.

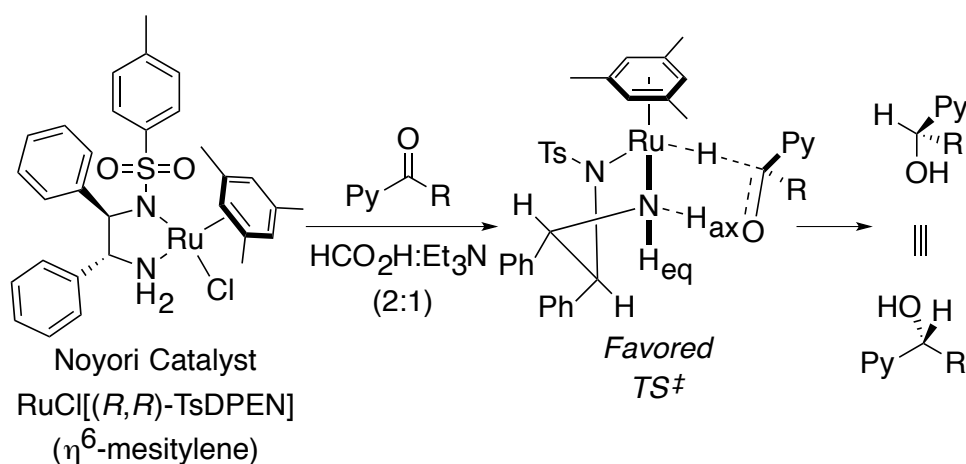


Figure IV.8: Stereochemistry of the Noyori reduction. Shown are the catalyst used, the preferred transition state of the catalyst and ketone and the alcohol generated after reduction. The predicted configuration of the alcohol is as shown.⁶⁰

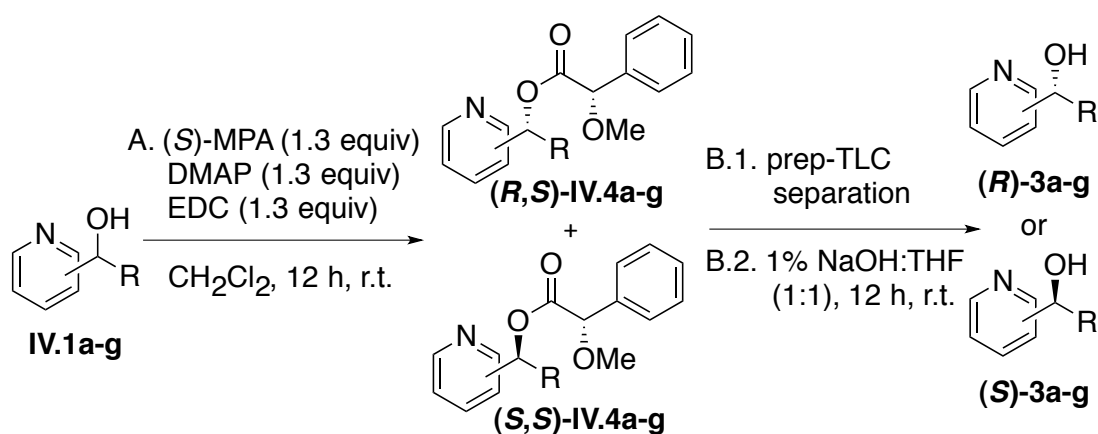
The asymmetric reduction was shown to provide (*R*)-1-(2-pyridyl) hexan-1-ol (**(*R*)-IV.3a**) in high yield. There was some concern however, that the reduction would not be equally as successful for α -aryl pyridyl methanones. The outcome of the Noyori reduction with Ru(η^6 -mestylene)-(*R,R*)-TsDPEN is known to be effected by the identity of the α -substituent in terms of both yield and enantioselectivity. It has been demonstrated that for acetophenone the corresponding alcohol is generated with a >99% yield and 97% *ee* whereas reduction of *p*-methoxyphenyl-*p*-cyanophenylketone under identical conditions provides a 54% yield and 66% *ee* of the corresponding alcohol.⁵⁹ Yet, the reduction was attempted with phenyl-2-pyridyl ketone. The starting ketone was recovered after several attempts. The CBS reduction of phenyl-2-pyridyl ketone was also attempted and again the ketone was recovered. Table IV.2

Entry	Starting Alcohol	Product	Yield %	Product	Yield %	% <i>ee</i>
1	IV.1a	IV.2a	70	IV.3a	54	>99
2	IV.1b	IV.2b	67	IV.3b	83	0
3	IV.1c	IV.2c	37	IV.3c	76	0
4	IV.1d	IV.2d	30	IV.3d	65	0
5	IV.1e	IV.2e	95	IV.3e	70	0
6 ^a	IV.1h	IV.2h	84	IV.3h	50	0

Table IV.2: Results of MnO₂ oxidations and Noyori asymmetric reductions. Percent *ee* determined by HPLC.

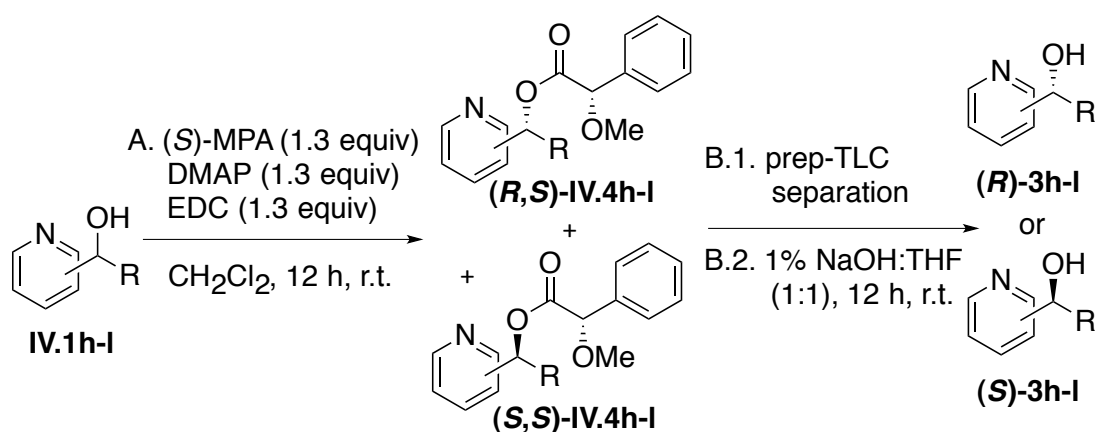
summarizes the results of the MnO₂ oxidations and subsequent Noyori reductions for the alkyl-pyridyl alcohols. Unfortunately, the only successful Noyori reduction was that to generate the test substrate ((*R*)-IV.3a). Therefore, other methods to obtain the chiral alcohols were explored. With the failure of the asymmetric reduction of the pyridyl ketones, HPLC separation of the racemic alcohol was attempted. This proved problematic for large scale separations. The retention times of the α -alkyl pyridyl alcohols enantiomers were too close to prevent a clean separation when concentrated samples were injected under different solvent mixtures, flow rates and with different chiral columns.

Finally, the separation of a diastereomeric mixture of the (*S*)-MPA esters of the racemic alcohol was attempted. This method was advantageous in that, the diastereomers of the alcohols could be separated by prep TLC and the absolute configuration of the alcohol was determined using the Mosher ester technique previously described.⁶⁶ The (*S*)-MPA esters were synthesized by EDC mediated coupling of the racemic alcohol with (*S*)- α -methoxy-phenylacetic acid and the resulting diastereomeric mixture was separated by prep TLC. The configuration of the pyridyl alcohol and diastereomeric ratio of the ester was determined from the ¹H NMR. The esters were subjected to hydrolysis with 1% NaOH in THF and the %*ee* of the alcohol was determined by HPLC prior to ECCD analysis. Table IV.3/4 summarizes the yields, *drs* and %*ee* for each of the alcohols obtained using this protocol.



Entry	Starting Alcohol	Product A	Yield %	Product B.1	Yield % (<i>dr</i> (R,S):(S,S))	Product B.2	Yield % (% ee)
1	IV.1a	IV.4a	99	(R,S)-IV.4a (S,S)-IV.4a	62 (4:1) 98 (0:1)	(R)-IV.3a (S)-IV.3a	86 (80) 99 (>99)
2	IV.1b	IV.4b	74	(R,S)-IV.4b (S,S)-IV.4b	75 (2:1) 56 (1:2)	(R)-IV.3b (S)-IV.3b	33 (ND) ^a 33 (ND)
3	IV.1c	IV.4c	67	(R,S)-IV.4c (S,S)-IV.4c	31 (4:1) 33 (0:1)	(R)-IV.3c (S)-IV.3c	NA >99 (>99)
4	IV.1d	IV.4d	56	(R,S)-IV.4d (S,S)-IV.4d	57 (1:0) 64 (0:1)	(R)-IV.3d (S)-IV.3d	71 (>99) 60 (>99)
5	IV.1e	IV.4e	77	(R,S)-IV.4e (S,S)-IV.4e	80 (2:1) 98 (0:1)	(R)-IV.3e (S)-IV.3e	51 (67) 64 (>99)
6	IV.1f	IV.4f	47	(R,S)-IV.4f (S,S)-IV.4f	71 (20:1) >99 (0:1)	(R)-IV.3f (S)-IV.3f	>99 (95) 89 (>99)
7	IV.1g	IV.4g	89	(R,S)-IV.4g (S,S)-IV.4g	45 (4:1) 50 (0:1)	(R)-IV.3g (S)-IV.3g	NA >99 (>99)

Table IV.3: Synthesis of (S)-MPA Esters and subsequent hydrolysis yielding chiral α -alkyl pyridyl alcohols. Absolute stereochemistry and diastereomeric ratios were determined by ^1H NMR. Enantiomeric excess was determined by chiral HPLC (AD-H, 96:4 hexanes:*i*PrOH, 0.5 mL/min). a: Enantiomers could not be resolved with HPLC. ND: Not determined. NA: Not Applicable.



Entry	Starting Alcohol	Product A	Yield %	Product B.1	Yield % (dr (R,S):(S,S))	Product B.2	Yield % (% ee)
1	IV.1h	IV.4h	96	(R,S)-IV.4h (S,S)-IV.4h	65 (10:1) 79 (0:1)	(R)-IV.3h (S)-IV.3h	96 (91) 99 (>99)
2	IV.1i	IV.4i	96	(R,S)-IV.4i (S,S)-IV.4i	>99 (3:1) 91 (0:1)	(R)-IV.3i (S)-IV.3i	76 (75) >99 (>99)
3	IV.1j	IV.4j	95	(R,S)-IV.4j (S,S)-IV.4j	>99 (10:1) >99 (1:20)	(R)-IV.3j (S)-IV.3j	>99 (91) >99 (95)
4	IV.1k	IV.4k	60	(R,S)-IV.4k (S,S)-IV.4k	>99 (10:1) >99 (1:20)	(R)-IV.3k (S)-IV.3k	37 (91) 29 (95)
5	IV.1l	IV.4l	99	(R,S)-IV.4l (S,S)-IV.4l	41 (4:1) 50 (0:1)	(R)-IV.3l (S)-IV.3l	>99 (80) >99 (>99)

Table IV.4: Synthesis of (S)-MPA Esters and subsequent hydrolysis yielding chiral α -aryl pyridyl alcohols. Absolute stereochemistry and diastereomeric ratios were determined by ^1H NMR. Enantiomeric excess was determined by chiral HPLC (AD-H, 96:4 hexanes:*i*PrOH, 0.5 mL/min).

In addition to the systematic study of pyridyl alcohols, an example illustrating the application of the ECCD analysis with a more complex molecule was desired. An isoquinoline containing natural product isolated in 2010 by Awang and co-workers from *Beilschmiedia brevipes* was chosen as an ideal candidate to show the extension of the ECCD methodology

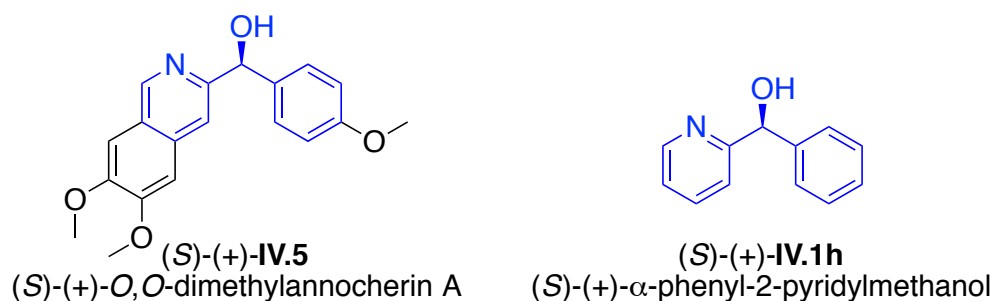
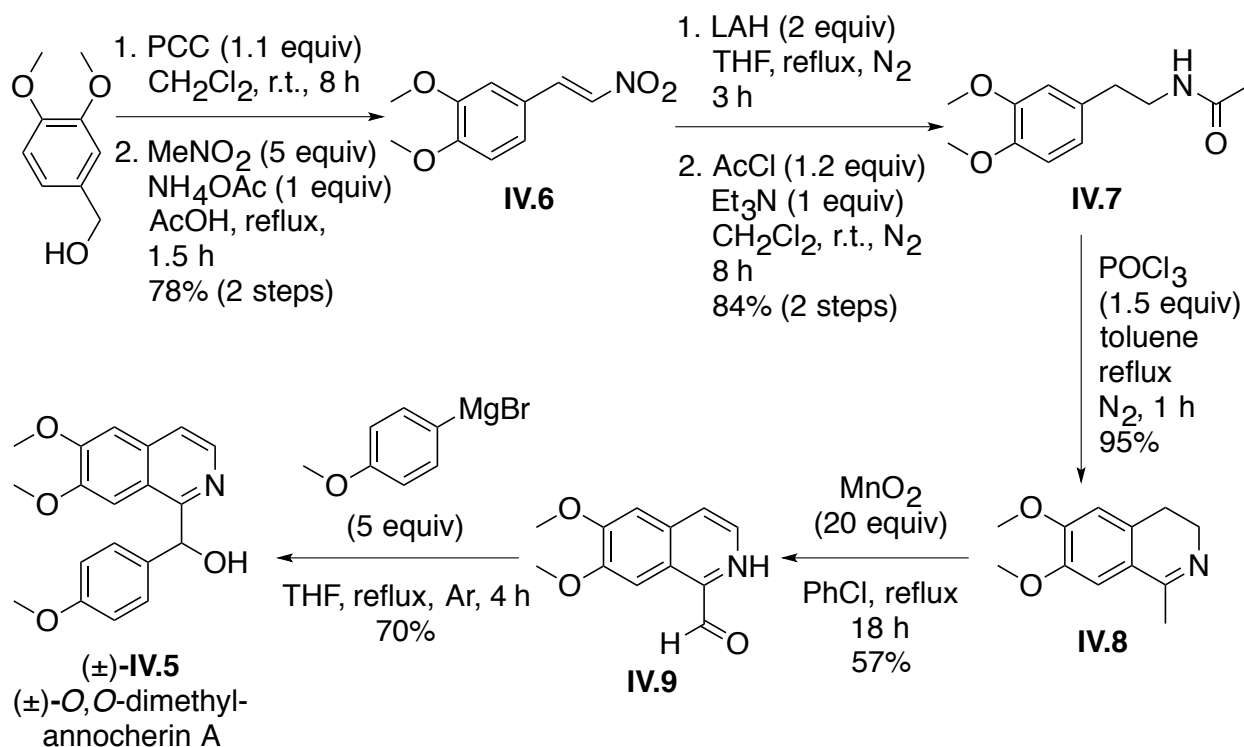


Figure IV.9: The structure of *O,O*-dimethylannocherin A.⁷⁰ The shared core of the natural product with (*S*)- α -phenyl-2-pyridylmethanol is highlighted in blue. These molecules are expected to have similar ECCD results.

from small chiral building blocks to molecules with greater complexity.⁷⁰ The structure *O,O*-dimethylannocherin A, as determined by NMR analysis, is a tris-methoxy substituted α -aryl isoquinoline alcohol (Figure IV.9). The authors determined the configuration of the naturally occurring enantiomer to be *S* through the ECCD protocol reported by Snatzke and co-workers.^{64,69} At the core of *O,O*-dimethylannocherin A is (*S*)- α -phenyl-2-pyridylmethanol therefore, it was hypothesized that the sign of the ECCD signal for the natural product and (*S*)-(+)- α -phenyl-2-pyridylmethanol should be the same.

The synthesis of *O,O*-dimethylannocherin A began with a PCC oxidation of the commercially available veratryl alcohol (3,4-dimethoxybenzyl alcohol) to veratryl aldehyde (Scheme IV.1). The aldehyde was then subjected to an aldol condensation with nitromethane providing the nitro styrene, (*E*)-1,2-dimethoxy-4-(2-nitrovinyl)benzene in 78% yield for the two steps.⁷¹ This was reduced to the saturated amine with LAH and protected with acetylchloride providing the *N*-acetyl-1,2-dimethoxy-4-(2-aminoethyl)benzene in 84% yield for the two steps. After some optimization, a POCl₃ catalyzed Bischler-Napieralski dehydrative cyclization gave a 95% yield of the dihydroisoquinoline.⁷² Initially, the dihydroisoquinoline was to be oxidized to



Scheme IV.1: Synthesis of racemic *O,O*-dimethylannocherin A.

the isoquinoline under dehydrogenation conditions and a second oxidation with SeO₂ to yield the desired isoquinoline aldehyde for the following Grignard addition. Oxidation of the dihydroisoquinoline was attempted under a variety of conditions (Table IV.5).⁷³⁻⁷⁶ Dihydroquinoline in the presence of air or oxygen in DMSO or DMA provided low yields of the isoquinoline with several unidentifiable decomposition products. Fortunately, oxidation of the dihydroisoquinoline with MnO₂ in refluxing chlorobenzene provided a separable mixture of the isoquinoline and the isoquinoline aldehyde.^{75,76} Further optimization of the MnO₂ oxidation was conducted by varying the amount of the oxidant present and changing the solvent. It was found that 20 equivalents of MnO₂ and chlorobenzene were best for generation of the desired aldehyde without significant decomposition. This route was chosen even though at most 30%

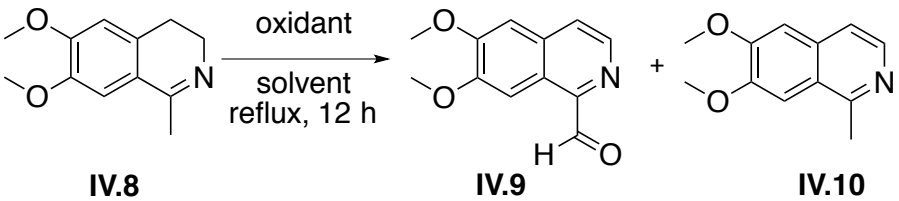
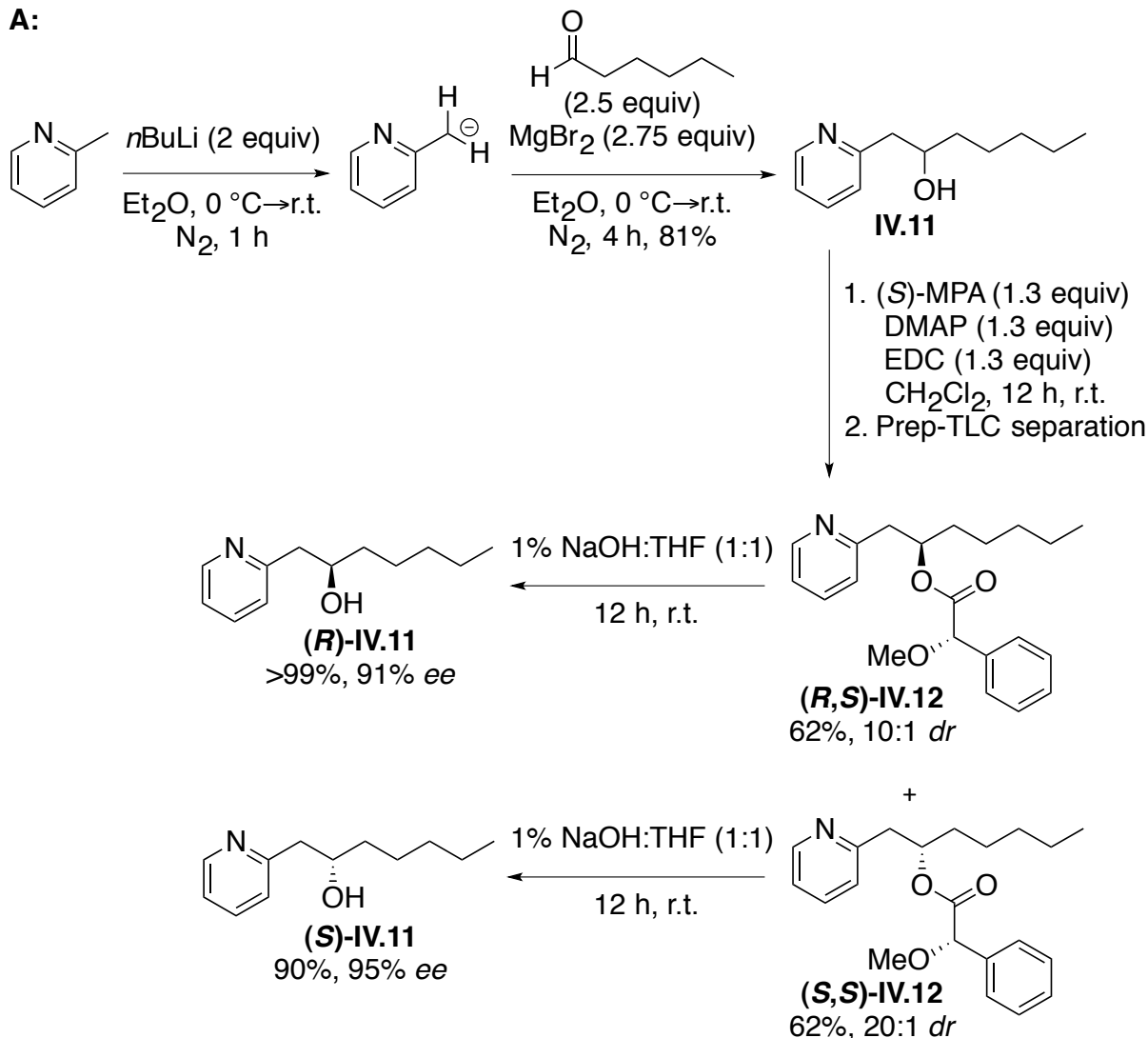
					
Entry	Oxidant	Solvent	Conv. %	IV.9:IV.10	Total Yield IV.9 + IV.10 (%)
1	air	DMSO	50	0:1	50
2	air	DMA	100	0:1	24
3	O ₂	DMSO	100	0:1	66
4	O ₂	DMA	100	0:1	18
5	MnO ₂ (10 equiv)	PhCl	100	1:2	75
6	MnO ₂ (20 equiv)	PhCl	100	2:1	73
7	MnO ₂ (30 equiv)	PhCl	100	1:1	72
8	MnO ₂ (85 equiv)	PhCl	100	ND	>5
9	MnO ₂ (20 equiv)	toluene	100	ND	12

Table IV.5: Optimization of dihydroisoquinoline oxidation.

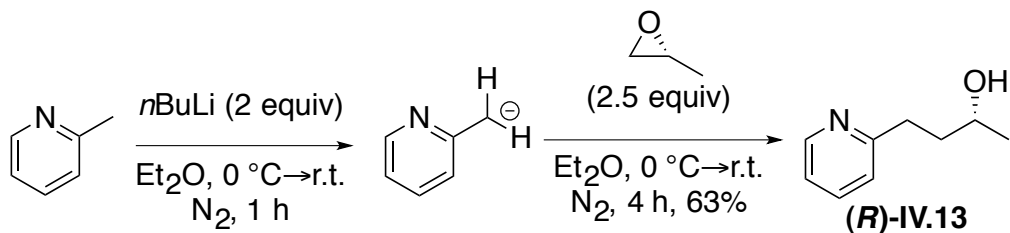
of the aldehyde was isolated. The purified isoquinoline was subjected to SeO₂ oxidation conditions however, only decomposition was observed.⁷⁷ With the aldehyde in hand, addition of *p*-methoxyphenylmagnesium bromide provided the racemic *O,O*-dimethylannocherin A. The enantiomers were separated by chiral HPLC.

With the completion of the synthesis of *O,O*-dimethylannocherin A, synthesis of the α -chiral pyridyl alcohols was concluded. Being that the ECCD analysis of the 1,*n*-glycols demonstrated that ECCD could be observed for substrates in which the binding sites are separated by a number of carbon units, pyridyl alcohols with the hydroxyl group moved to the β - or γ -carbon were also synthesized (Scheme IV.2). The anion of 2-picoline is easily generated

A:



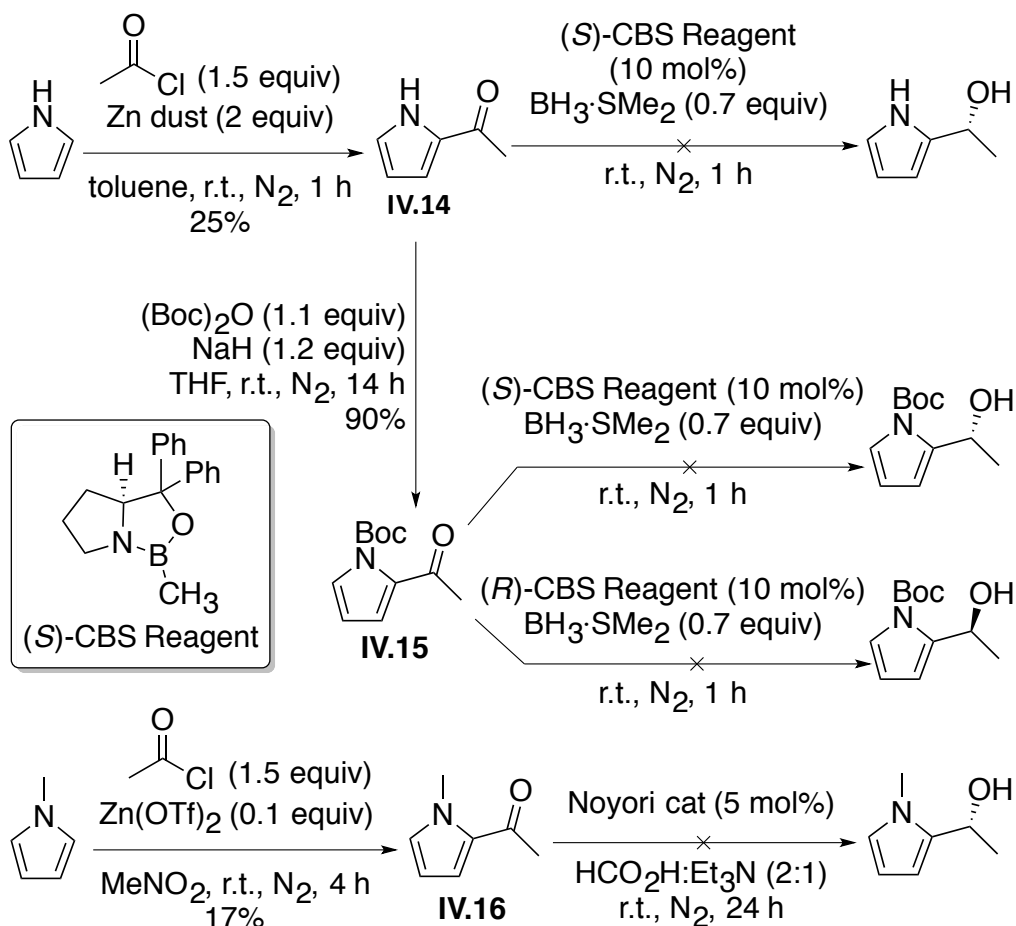
B:



Scheme IV.2: Synthesis of β - and γ -pyridyl alcohols. **A:** Addition of hexanal to 2-picolate anion and subsequent MPA ester generation separation and hydrolysis. **B:** Addition propylene oxide to 2-picolate anion.

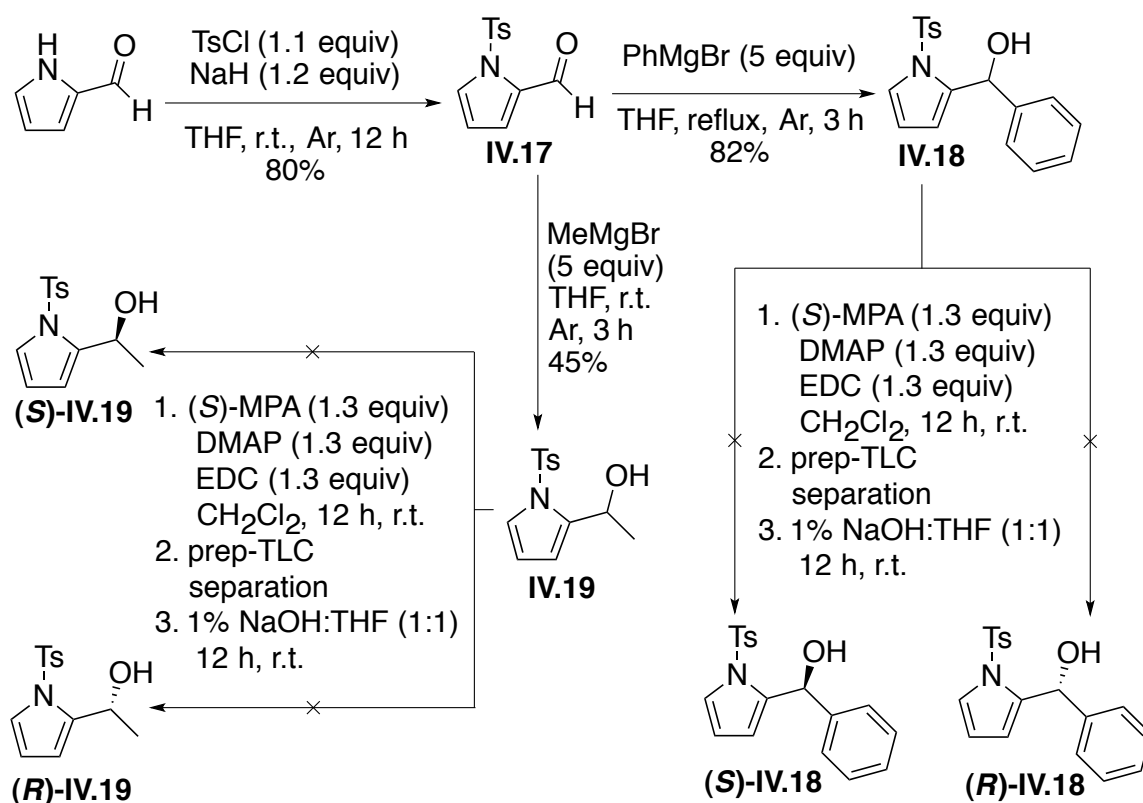
by deprotonation of the α -methyl with *n*-butyllithium.^{78,79} Addition of hexanal to the 2-picolate anion provided the racemic β -hydroxypyridine, 1-(2-pyridyl)-heptan-2-ol (**IV.11**) in 81% yield. The addition of (*R*)-propylene oxide to the 2-picolate anion gave the γ -hydroxypyridine, (2*R*)-4-(2-pyridyl)-butan-2-ol (**IV.12**) in 63% yield. The stereochemistry of **IV.11** was determined using the Mosher ester protocol described for the α -chiral pyridyl alcohols.

With these pyridine based chiral alcohols at hand, expansion of the substrate scope to other heteroaromatic alcohols was desired. Initial attempts to synthesize the pyrrole and furan based alcohols proved problematic. With pyrrole and furan readily available, a two-step Friedel-Crafts acylation to install an acetyl group followed by asymmetric reduction using a CBS or Noyori asymmetric reduction was envisioned. Friedel-Crafts acylation of pyrrole with acetylchloride and zinc dust provided a mixture of 2- and 3-acetylpyrrole (Scheme IV.3). These were separable by column chromatography to give 25% yield of the 2-acetylpyrrole (**IV.14**).^{80,81} The CBS reduction of **IV.14** was attempted but the desired alcohol was not generated. It was hypothesized that the free nitrogen of the pyrrole could be coordinating with the boron of the catalyst thereby preventing the reduction of the ketone. Thus, the pyrrole was subjected to Boc protection.⁸¹ The CBS reduction of the *N*-Boc-2-acetylpyrrole (**IV.15**) was attempted again however, the ketone was recovered. *N*-Methylpyrrole was also available and acetylation with acetylchloride and zinc II triflate gave *N*-methyl-2-acetylpyrrole (**IV.16**) in 20% yield.⁸² This ketone was subjected to Noyori reduction conditions. Unfortunately, again there was no evidence of the desired alcohol by NMR.



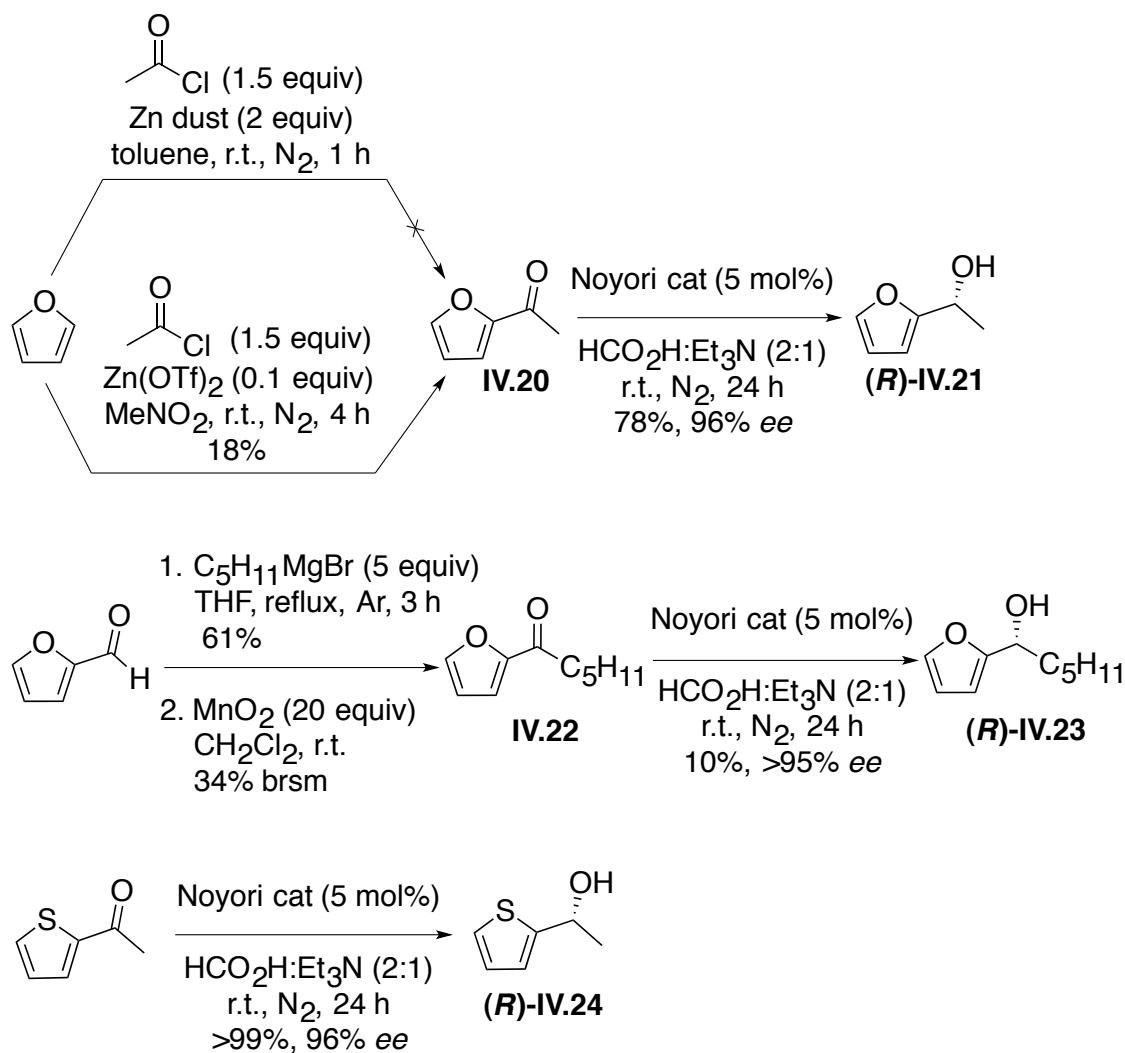
Scheme IV.3: Failed attempts to synthesize of α -hydroxy pyrroles using asymmetric reductions.

In other attempts to generate a pyrrolyl alcohol, pyrrole-2-carboxaldehyde was protected with tosyl chloride, generating *N*-tosyl-pyrrole-2-carboxaldehyde (IV.17) then addition of phenylmagnesium bromide provided racemic α -(*N*-tosyl-2-pyrrolyl)-benzylalcohol (IV.18) in 66% yield for the two steps (Scheme IV.4). Similarly, addition of methylmagnesium bromide to the pyrrolylaldehyde gave α -(*N*-tosyl-2-pyrrolyl)-ethanol (IV.19) in 36% yield overall. These two racemic alcohols were subjected to MPA esterification then separation by prep-TLC. Unfortunately, neither the ester or the alcohol (in the event that hydrolysis occurred on the TLC) were detected. At this point the synthesis of α -chiral pyrrolyl alcohols was abandoned.



Scheme IV.4: Synthesis of the α -hydroxy pyrroles following the protocol for α -hydroxy pyridines. Chiral alcohols were to be accessed through MPA esterification, separation of diastereomers then basic hydrolysis of the ester. Ultimately this was unsuccessful.

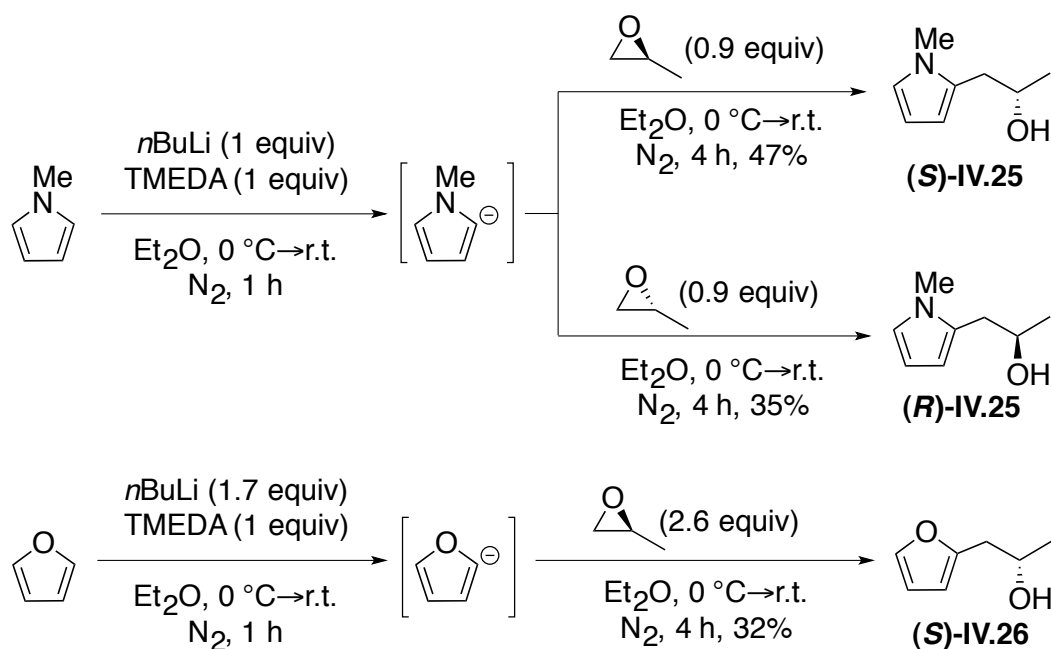
Similar methodologies were then employed for the synthesis of the furan based chiral alcohols (Scheme IV.5). Friedel-Crafts acylation was attempted with furan to generate 2-acetylfuran. The use of acetylchloride in the presence of zinc II triflate generated 2-acetylfuran (**IV.120**) in 18% yield.⁸² The subsequent Noyori reduction was successful providing the alcohol, (**R**)-**IV.21**, in 78% yield and 96% *ee*.⁸³ A second furyl alcohol was synthesized from furan-2-carboxaldehyde following the Grignard addition, MnO_2 oxidation⁸⁴, Noyori reduction described for the pyridyl alcohols. The chiral alcohol, 1*R*-(2-furyl)-hexan-1-ol (**(R)-IV.23**), was isolated in 2% yield overall and >95% *ee* based on optical rotation.⁸⁵ Finally, 1*R*-(2-thiophenyl)-ethan-1-ol



Scheme IV.5: Synthesis of chiral furyl alcohols. These were accessed by Noyori reduction of the corresponding ketones.

((R)-IV.24) was isolated in >99% yield and 96% ee (based on optical rotation) from the Noyori reduction of the commercially available 2-acetylthiophene.⁸⁶

N-methylpyrrole and furan were also functionalized with a β-hydroxy alkyl substituent by directed deprotonation with *n*BuLi in the presence of TMEDA (Scheme IV.6).⁸⁷ Optically pure propylene oxide was then added to the anion generating (2*S*)-1-(2-*N*-methylpyrrolyl)-propan-2-ol (**((S)-IV.25)**), (2*R*)-1-(2-*N*-methylpyrrolyl)-propan-2-ol (**((R)-IV.25)**), and (2*S*)-1-(2-furyl)-



Scheme IV.6: Synthesis of 1-(2-*N*-methylpyrrolyl)-propan-2-ol and 1-(2-furyl)-propan-2-ol using a TMEDA directed deprotonation.

propan-2-ol ((S)-IV.26)⁸⁸ in moderate yields. This completed the synthesis of the chiral heteroaromatic alcohols for this study.

IV.4: ECCD Study of the Chiral Heteroaromatic Alcohols

With the substrates in hand, the UV-Vis and ECCD studies were conducted. Initially, a UV-Vis titration with 2-picoline was conducted to obtain the Soret band shift (11 nm) and the binding constant for an sp^2 nitrogen ($1.5 \times 10^5 \text{ M}^{-1}$) with the C8-Zn-TPFP-Tweezer (see experimental for graphs from UV-Vis titration and binding constant calculation⁸⁹). The Soret shift (6 nm) and binding constant (10^5 M^{-1}) for a monoalcohol was previously determined.⁸ The combination of this data indicates that for any pyridyl alcohol complexes, a maximum Soret band shift of 11 nm can be expected. Also, the binding constant data shows that the pyridine

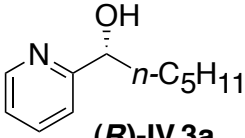
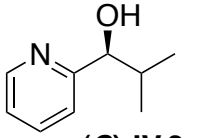
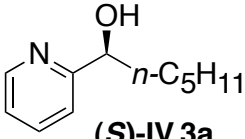
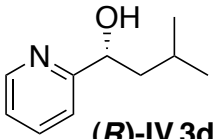
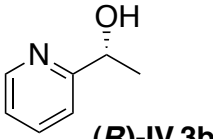
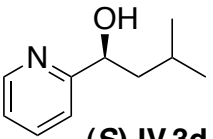
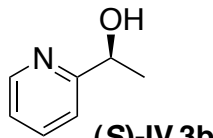
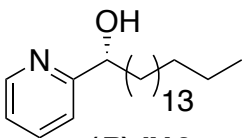
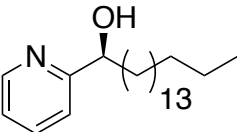
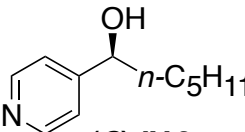
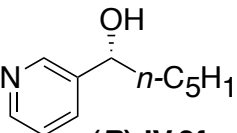
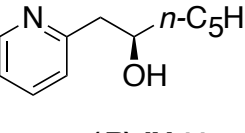
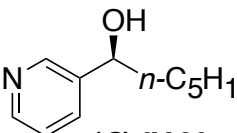
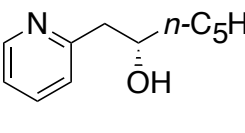
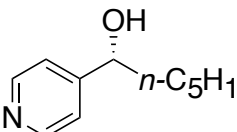
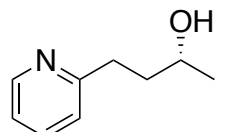
Entry	Pyridyl Alcohol	Expected Sign	Observed ECCD λ nm ($\Delta\epsilon$)	Entry	Pyridyl Alcohol	Expected Sign	Observed ECCD λ nm ($\Delta\epsilon$)
1	 (R)-IV.3a 80% ee	⊖	428 (-30) 414 (+31) A = -61	5a	 (S)-IV.3c > 95% ee	⊕	428 (+35) 415 (-22) A = +57
2	 (S)-IV.3a > 95% ee	⊕	428 (+74) 414 (-49) A = +123	6a	 (R)-IV.3d > 95% ee	⊖	425 (-32) 418 (+28) A = -60
3	 (R)-IV.3b 66% ee	⊖	No ECCD	7a	 (S)-IV.3d > 95% ee	⊕	426 (+51) 415 (-34) A = +85
4	 (S)-IV.3b 66% ee	⊕	No ECCD	8b	 (R)-IV.3e > 95% ee	⊖	429 (-26) 414 (+22) A = -48

Table IV.6: ECCD data for alkyl substituted chiral pyridyl alcohols. The expected signs are a result of the mnemonics developed. All measurements: hexanes, 0 °C, 2 μ M tweezer, 10 equivalents of substrate. a: 60 equivalents of substrate. b: 2 equivalents of substrate.

Table IV.6 (cont'd): ECCD data for alkyl substituted chiral pyridyl alcohols. The expected signs are a result of the mnemonics developed. All measurements: hexanes, 0 °C, 2 μ M tweezer, 10 equivalents of substrate. a: 60 equivalents of substrate. b: 2 equivalents of substrate.

Entry	Pyridyl Alcohol	Expected Sign	Observed ECCD λ nm ($\Delta\epsilon$)	Entry	Pyridyl Alcohol	Expected Sign	Observed ECCD λ nm ($\Delta\epsilon$)
9	 (S)-IV.3e 66% ee	⊕	429 (+90) 415 (-61) A = +151	13	 (S)-IV.3g > 95% ee	⊖	426 (-198) 415 (+111) A = -309
10 ^b	 (R)-IV.3f 95% ee	⊖	427 (-48) 415 (+64) A = -112	14	 (R)-IV.11 90% ee	⊕	429 (+85) 414 (-38) A = +88
11	 (S)-IV.3f > 95% ee	⊕	425 (+26) 417 (-33) A = +59	15	 (S)-IV.11 95% ee	⊖	427 (-43) 415 (+43) A = -86
12	 (R)-IV.3g 80% ee	⊕	426 (+234) 415 (-127) A = +361	16	 (R)-IV.12 > 95% ee	⊕	422 (+28) 411 (-17) A = +45

nitrogen binds with the zinc center of the porphyrins approximately as strong as the hydroxyl oxygen.

Next, the ECCD study of the pyridyl alcohols was conducted. As the test substrate provided ECCD in hexanes at 0 °C, these conditions were used for the initial screening of the pyridyl alcohols. Table IV.6 summarizes the ECCD data obtained for the alkyl substituted pyridyl alcohols. All of the alcohols provided ECCD signals with the exception of 1-(2-pyridyl)ethan-1-ols, (*R*)-**IV.3b** and (*S*)-**IV.3b**. This is likely due to the low enantiomeric excess for these alcohols. For the other 2-pyridyl and the 3-pyridyl alcohols, a clear trend was observed. Those alcohols bearing an (*R*) configuration provided a negative ECCD and the (*S*) alcohols generated positive ECCD. Figure IV.10 provides the overlay of the ECCD signals for the enantiomers of 1-(2-

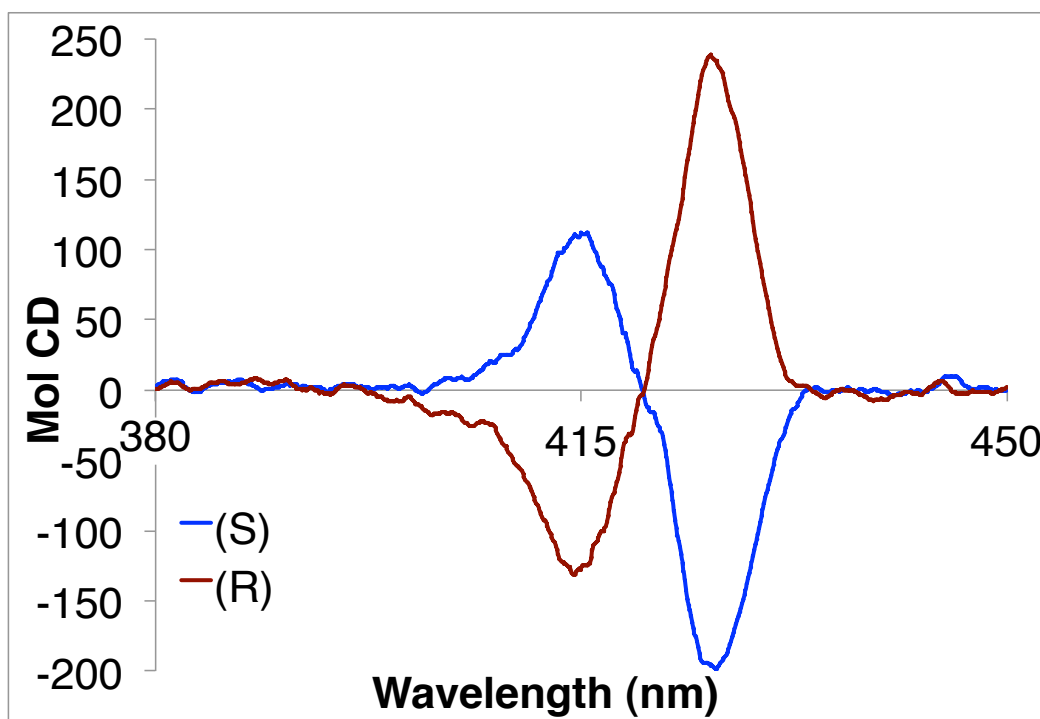


Figure IV.10: Overlay of the ECCD signals for the enantiomers of 1-(4-pyridyl)hexan-1-ol (**IV.3g**) with C8-Zn-TPFP-Tweezer. The measurements were taken in hexanes at 0 °C at 2 μ M tweezer with 10 equivalents of pyridyl alcohol.

pyridyl)-hexan-1-ol. The enantiomers provided ECCD signals of the opposite sign and approximately equal intensity as expected.

From this data a mnemonic was developed and is shown in Figure IV.11. A thorough analysis of conformation of the alcohol was conducted to determine the most likely conformation when bound to the tweezer. First, Figure IV.11 A considers the possibility of eclipsed and gauche rotomers about the bond between carbon 2 of the pyridine and the α -carbon. Eclipsed will be higher in energy due to steric interactions between the ring (carbons 3 and 4) with the substituents of the α -carbon. Therefore the eclipsed rotomers were no longer considered as possible conformers to bind with the tweezer. Next, all six rotomers of the gauche conformation had to be considered. Figure IV.11 B shows each conformer and the proposed approach of the porphyrins to the binding functionalities. The porphyrins are represented by the green and blue arrows with the labels P1 and P2, respectively. Those conformers that placed the binding groups parallel such that the porphyrins would have to approach the same face of the molecule were eliminated, specifically **A.3.b**, **A.4.a** and **A.4.b**. Sterically, it is highly disfavored for the porphyrins to bind to the same face of a molecule as the porphyrins are very large (14 Å across). Then, the conformers that placed the large R group parallel to the nitrogen were also eliminated (**A.3.c** and **A.4.c**). The R group in this location would interfere with the porphyrin binding with the pyridine nitrogen lone pair electrons as these groups would be parallel to one another. This eliminated all of the possible conformers except **A.3.a**. This conformer has the two binding groups anti-parallel thus, the porphyrins would approach from opposite sides of the molecule. Also, the small hydrogen is parallel to the

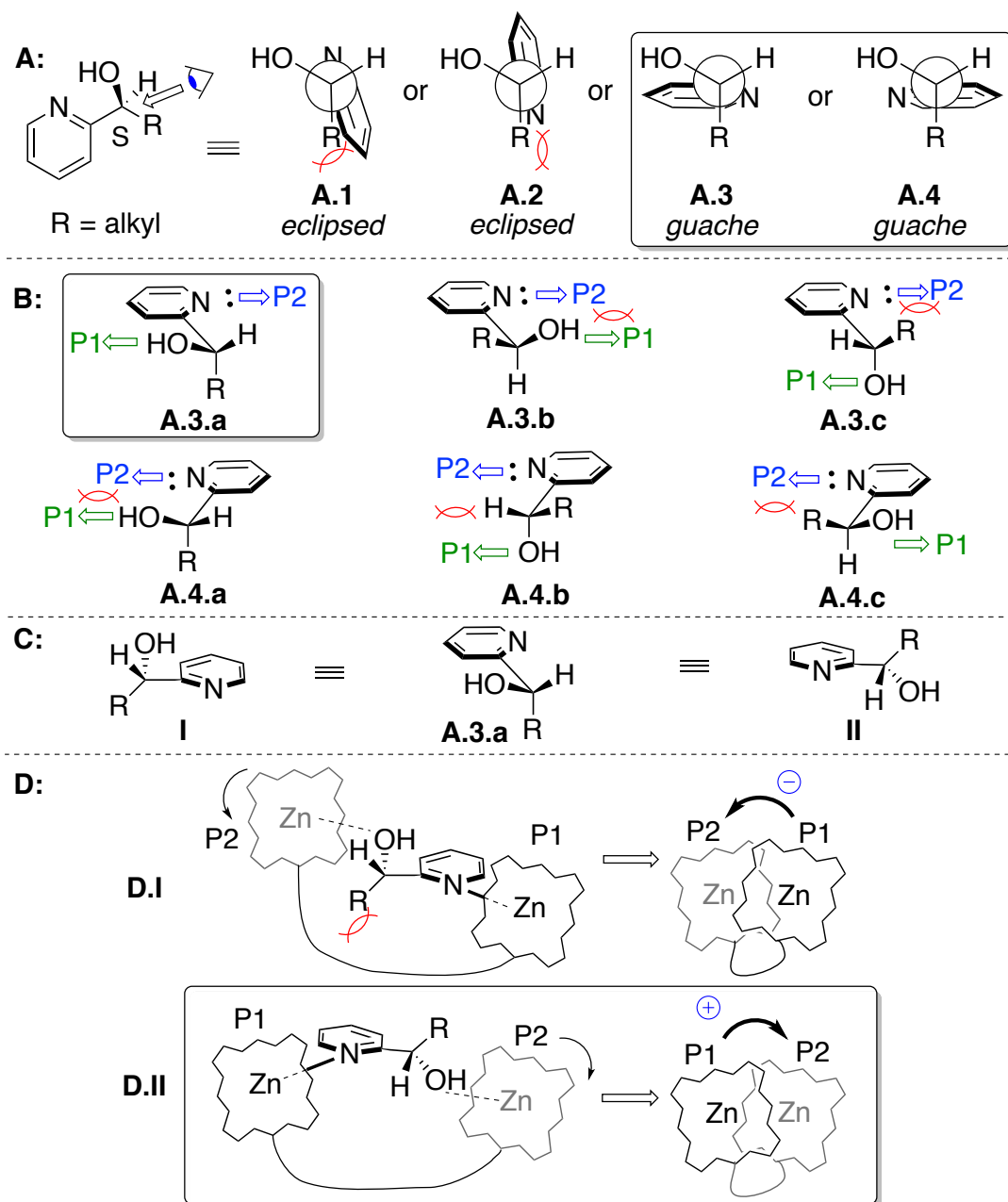


Figure IV.11: Proposed mnemonic for α -alkyl substituted 2-pyridyl and 3-pyridyl alcohols. Shown is an (*S*) alcohol. See text for the detailed explanation. **A:** Eclipsed and gauche rotomers about the pyridine-C2/ α -carbon bond. **B:** All possible gauche rotomers and approach of the porphyrins when bound. **C:** Different views of the most likely rotomer bound with the tweezer. **D:** There are two possible binding modes with the tweezer. **D.II** is most likely due to least steric interactions.

nitrogen lone pair electrons. The hydrogen is not expected to interfere with binding to the porphyrin like the larger R group.

Figure IV.11 C is simply three different ways in which **A.3.a** can be drawn. **I** is the original drawing is rotated 90° clockwise in the plane perpendicular to the plane of the paper. **II** is a 180° rotation of **I** in the plane of the paper. Then **I** and **II** are bound to the tweezer as shown in Figure IV.11 **D.I** and **D.II**. In both cases, the front porphyrin, P1 (shown in black), will bind with the lone pair electrons of the pyridine nitrogen such that the plane of the porphyrin is parallel to the R group of the α -carbon. The back porphyrin, P2 (shown in grey), will bind with the lone pair electrons of the hydroxyl again, the plane of this porphyrin will be parallel to the R group of the α -carbon. The linker between the porphyrins will wrap under the α -face of the pyridine. The resulting helicity of the porphyrins will be a result of the steric interaction between P2 and the pyridine-C3 that will force P2 to rotate. For **D.I** an overall counterclockwise helicity from P1 to P2 is expected and a negative ECCD signal should be observed. The opposite is expected for **D.II**. P2 will rotate clockwise to avoid the pyridine-C3 resulting in an overall clockwise helicity from P1 to P2 and a positive ECCD signal would be generated. The difference between **D.I** and **D.II** is the location of the linker relative to the R group of the α -carbon. For **D.I**, the R group is oriented on the α -face of the pyridine therefore, R and the linker are both oriented under the plane of the pyridine. It is expected that there will be a unfavorable steric interaction between the linker and the R group of the α -carbon. However, for **D.II** the R group is oriented on the β -face of the pyridine, opposite of the linker and there will be no interaction between the R group and the linker. Therefore, **D.II** is thought to be the most likely conformation of the tweezer/pyridinol complex. This complex incorporates **A.3.a**, the

conformer of the pyridinol thought to be most favored for binding with the tweezer. Furthermore, once bound with the tweezer, the R group is opposite the linker to reduce steric interactions. **D.II** exhibits a clockwise helicity of the porphyrins which predicts a positive ECCD signal. This matches well with the observed ECCD for (*S*) substrates (Table IV.5). Following this mnemonic, a counterclockwise helicity of the porphyrins and a negative ECCD would be expected for the (*R*) substrates (not shown).

This model explains the results of the C2- and C3- substituted α -alkyl pyridinols. It should be noted that complexation with the tweezer could influence the energies of the conformers shown. Therefore, it is possible that another rotomer is favored for ECCD but, based on the energetics of the substrate alone, D.II is believed to be the favored complex for these substrates.

The C4-substituted substrates did not match this prediction. After further consideration, it was thought that the location of the binding sites was likely influencing the binding mode and the observed sign. Chapter 3 describes and explores the side-on and head-on binding modes of the Zn-TPFP-tweezers. For the C2- and C3- pyridinols, the relative location of the lone pair electrons of the pyridine and hydroxyl group being anti-parallel from the bond between the pyridine-C2 to α -carbon would predict a side-on binding mode. But for C4- α -alkyl pyridinols, the nitrogen of the pyridine (also the lone pair electrons of the pyridine nitrogen) and the α -carbon lie along the same line as the bond between the pyridine-C4 to α -carbon. This substitution pattern would likely prefer a head-on binding mode as dictated by the orientation of the binding functionalities.

Figure IV.12 summarizes the conformational considerations when developing a binding model for the C4- α -alkyl pyridinols. First off, only the gauche conformers were considered as, eclipsed conformations are typically higher in energy. Figure IV.12 A shows the two starting points for the gauche conformers. Figure IV.12 B provides all the possible rotomers of the two gauche conformers. The rotomers **A.1.b**, **A.1.c**, **A.2.b** and **A.2.c** were all eliminated as the rotomer bound with the tweezer suffers A^{1,3} strain between the R group of the α -carbon and the pyridine-C3. This leaves **A.1.a** and **A.2.a** as the rotomers under consideration for binding with the tweezer. There will still be A^{1,3} strain between the hydroxyl group of the α -carbon and the pyridine-C3 but this should be considerably smaller than the strain associated with the R group as the hydroxyl is a sterically smaller group. The A value of a hydroxyl is 1.0 kcal/mol whereas the A value of an ethyl group is 1.75 kcal/mol. Note that these A values could be influenced by the conditions of the titration but it is thought that the hydroxyl is the smaller group under the ECCD conditions. Thus situating the large group in the least sterically congested location is energetically favored. Figure IV.12 C depicts the **A.1.a** and **A.2.a** conformers bound with the tweezer. For both complexes, **C.I** and **C.II**, the porphyrin P2 approaches the lone pair electrons of the pyridine nitrogen from the back such that the plane of the porphyrin lies in the plane of the paper. There are no steric influences on this porphyrin so, it will remain static in that location. The steric discrimination occurs with P1. For both complexes, the porphyrin P1 approaches the hydroxyl such that the plane of the porphyrin is in the plane of the paper but, this porphyrin will rotate to reduce interactions with the R group. In **C.I**, the porphyrin rotates counterclockwise resulting in an overall clockwise helicity of the porphyrins from P1 to P2 and a positive ECCD would be expected. The opposite arrangement is

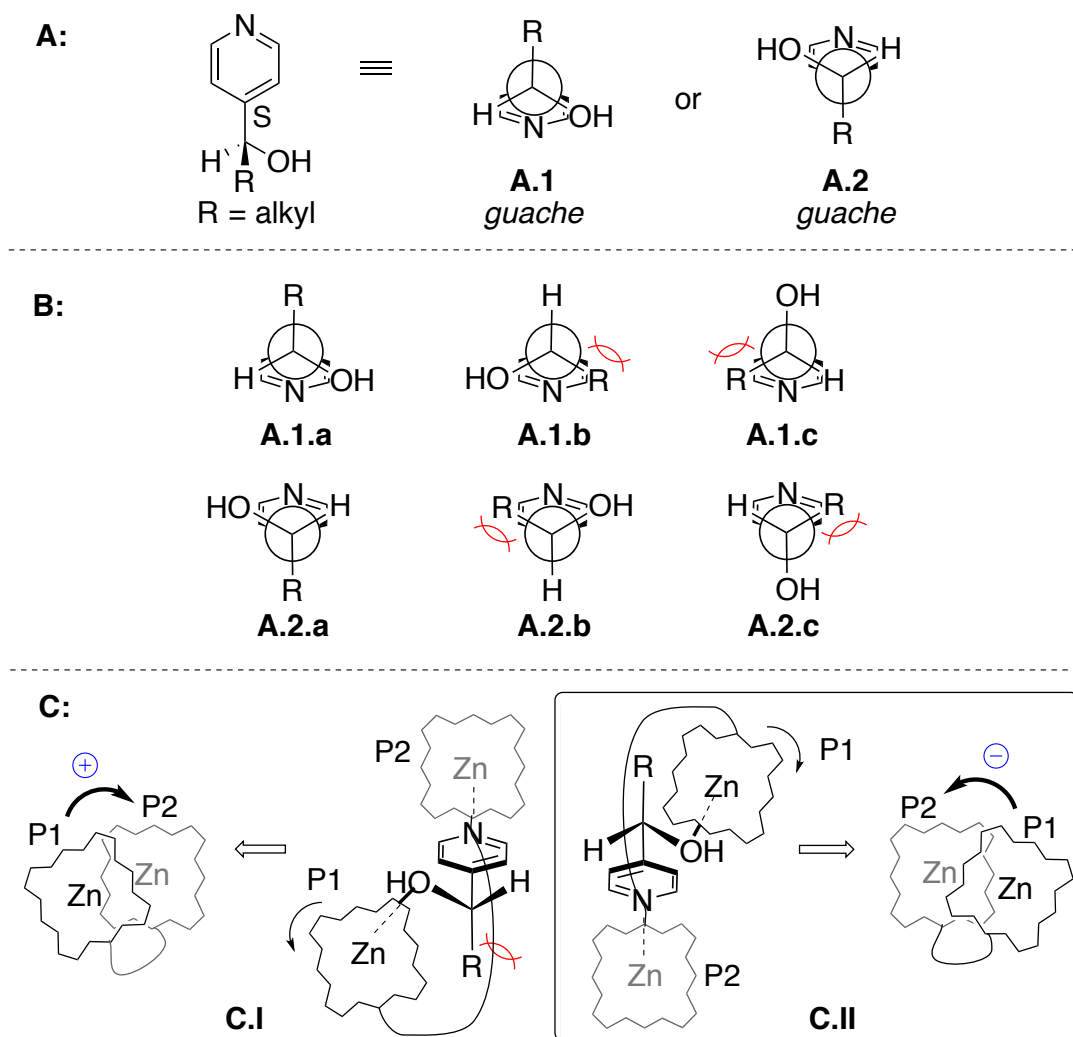


Figure IV.12: Proposed mnemonic for α -alkyl substituted 4-pyridyl alcohols. Shown is an (S) alcohol. See text for the detailed explanation. **A:** Guache rotomers about the pyridine-C4/ α -carbon bond. **B:** All possible guache rotomers. **C:** There are two possible complexes with the tweezer and the most favored pyridinol rotomers. **C.II** is most likely due to least steric interactions.

expected for **C.II**. The porphyrin, P1, will rotate clockwise to produce an overall counterclockwise arrangement of the porphyrins from P1 to P2 thus a negative ECCD is expected. Much like with the C2- and C3- substituted α -alkyl pyridinols, the complex **C.I** was

eliminated as the favored complex due to possible interactions between the R group and linker of the tweezer. Therefore, **C.II** is thought to be the favored complex and a negative ECCD would be expected for the (*S*) alcohol. Furthermore, the (*R*) alcohol is expected to provide a positive signal. This prediction from the binding model matches well with the observed ECCD for the C4- α -alkyl pyridinols.

The other alkyl substituted pyridinols (at the β - and γ -carbons) did not follow the mnemonic established for the α -alkyl pyridinols either. The β - and γ -substituted pyridinols have a larger degree of freedom, which must be considered to develop a mnemonic for these complexes. Figure IV.13 summarizes the proposed binding models for the β - and γ -substituted pyridinols. First, consider the β -alkyl pyridinol (Figure IV.13 A). The rotation about the pyridine-C2/ α -carbon bond would adopt the gauche conformation in **A.2**. For this conformer, the small hydrogens are in the most sterically congested location with the large alkyl group perpendicular to the pyridine in the least sterically encumbered location. The eclipsed conformation, **A.1**, is eliminated as large steric interactions between the pyridine and the substituents of the chiral center are expected in this conformation. Next, the rotomers of the α -carbon to β -carbon bond were considered. Again, only staggered conformations were considered as these are lower in energy than the eclipsed conformations. There are three rotomers of this bond. For two of the rotomers, **A.2.b** and **A.2.c**, the two binding functionalities, the pyridine and the hydroxyl, are located on the same face of the molecule. Thus the porphyrins would approach the binding sites from the same face, as indicated by the green and blue arrows. As discussed above, this is unfavorable and unlikely due to the size of the porphyrin. Therefore, the **A.2.a** rotomer that positions the binding groups anti to one another is favored. The combination of the **A.2** and **A.**

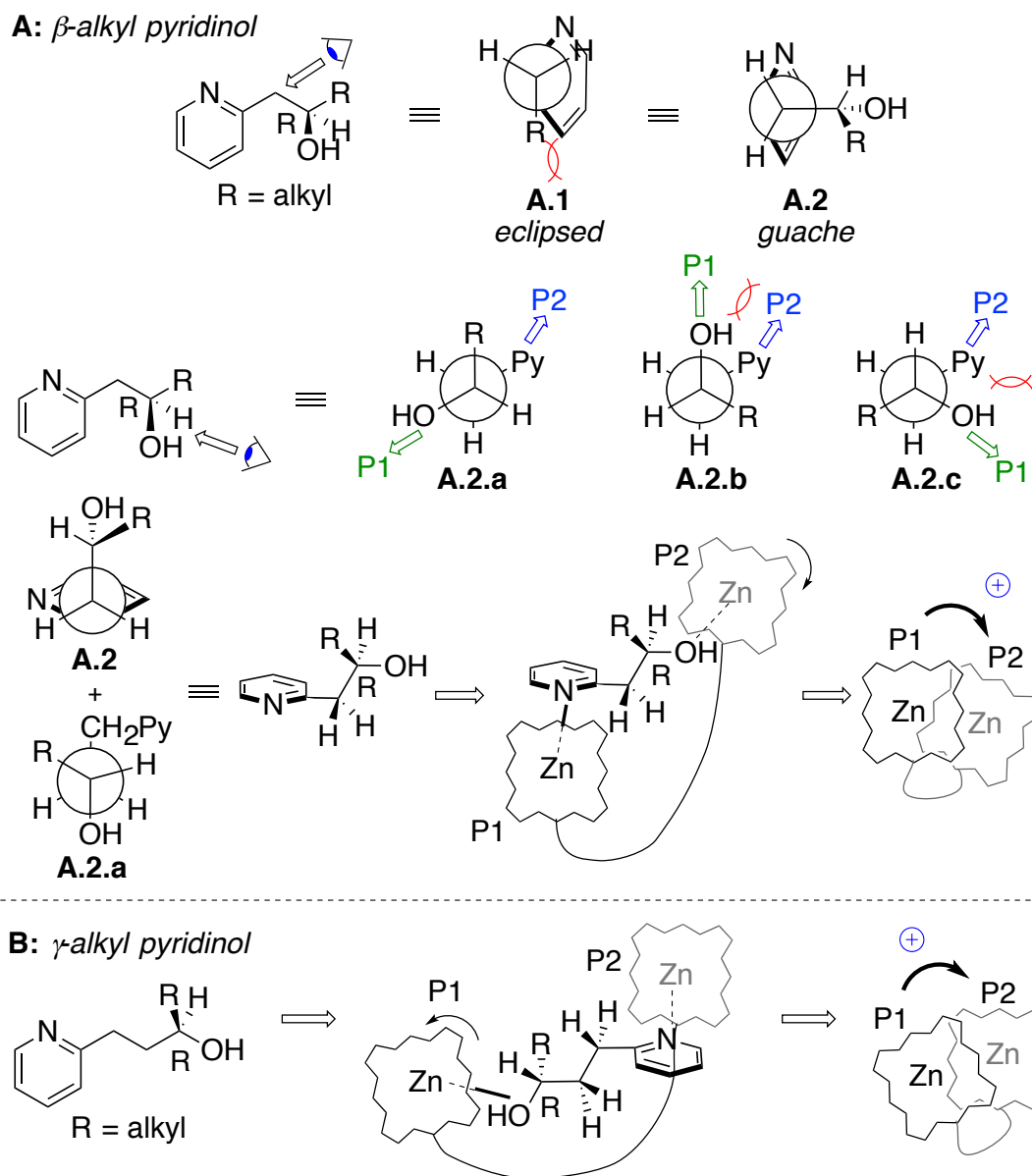


Figure VI.13: Binding mnemonic for β and γ -pyridinols. See text for detailed explanation. The (*R*) alcohols are shown for each. **A:** β -alkyl pyridinol: Eclipsed and gauche conformers about the pyridine-C2/ α -carbon bond. The three gauche rotomers of the α -carbon to β -carbon bond. The approach of the porphyrins is indicated by the green and blue arrows. Binding with the most favored conformer would generate a positive ECCD. **B:** γ -alkyl pyridinol: Similar analysis would indicate the conformer in the complex as most favored. This would provide a positive ECCD signal.

2.a Newman projections gives the three-dimensional representation of the alcohol which is thought to be the conformation that is preferred when bound to the tweezer. As before, P1 approaches the front of the molecule with the plane of the porphyrin in the plane of the paper and binds with the lone pair electrons of the pyridine nitrogen. This porphyrin may rotate away from the C2-substituent in a counterclockwise fashion. The porphyrin P2 then approaches the back face of the molecule again with the plane of the porphyrin in the plane of the paper. This porphyrin binds with the hydroxyl, *anti* to the R group. This porphyrin rotates in a clockwise fashion to minimize steric interaction with the pyridine ring. Overall there is a clockwise helicity of the porphyrins from P1 to P2. A clockwise helicity would generate a positive ECCD bisignate curve for the (*R*) substrate. This agrees with the observed ECCD signals for the enantiomers of 1-(2-pyridyl)-heptan-2-ol (**IV.11**). A similar analysis of the possible conformations of 4-(2-pyridyl)-butan-2-ol (the γ -alkyl pyridinol, **IV.12**) was conducted. The model shown in Figure IV. 13 B is thought to be the most favored conformation. When bound to the tweezer, a clockwise helicity of the porphyrins from P1 to P2 and a positive ECCD signal is predicted. Again, this agrees with the observed ECCD.

Table IV.7 summarizes the ECCD data observed for the aromatic substituted pyridyl alcohol. Unfortunately, the alcohols at the C2-position of the pyridine provided weak or no ECCD signal. The mesityl substituted alcohols, **IV.1i**, generated noisy ECCD signals of opposite sign and equal intensity. The weak or unobservable ECCD for these aromatic substrates is likely due to the increased sterics around the alcohol as aryl substituents are generally larger than alkyl substituents. The A value of an isopropyl substituent is 2.15 kcal/mol and the phenyl group is 3.0 kcal/mol. Therefore, the large substituent could be inhibiting binding with the

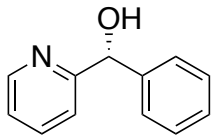
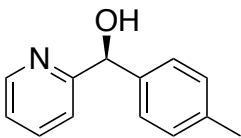
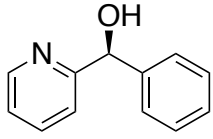
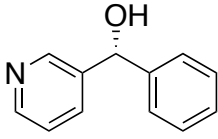
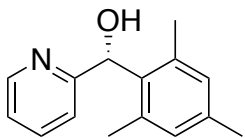
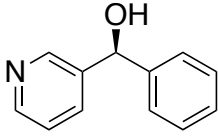
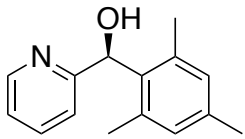
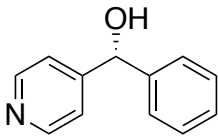
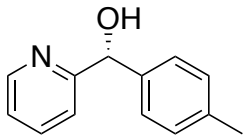
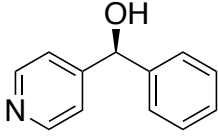
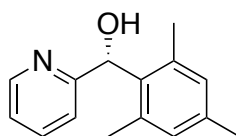
Entry	Pyridyl Alcohol	Expected Sign	Observed ECCD λ nm ($\Delta\epsilon$)	Entry	Pyridyl Alcohol	Expected Sign	Observed ECCD λ nm ($\Delta\epsilon$)
1	 (R)-IV.1h 90% ee	⊖	NO ECCD	6	 (S)-IV.1j 95% ee	⊕	NO ECCD
2	 (S)-IV.1h > 95% ee	⊕	NO ECCD	7	 (R)-IV.1k 90% ee	⊖	426 (+106) 413 (-40) A = +146
3	 (R)-IV.1i 75% ee	⊖	422 (+24) 415 (-14) A = +38	8	 (S)-IV.1k 95% ee	⊕	426 (-149) 413 (+93) A = -242
4	 (S)-IV.1i > 95% ee	⊕	423 (-18) 414 (+16) A = -34	9	 (R)-IV.1l 80% ee	⊕	426 (+239) 414 (-121) A = +360
5	 (R)-IV.1j 90% ee	⊖	NO ECCD	10	 (S)-IV.1l > 95% ee	⊖	426 (-479) 414 (+296) A = -775

Table IV.7: ECCD data for the aryl substituted pyridyl alcohols. The expected sign is based on the mnemonics developed for the alkyl pyridyl alcohols. All measurements: hexanes, 0 °C, 2 μ M tweezer, 1 equivalents of substrate. a: 60 equivalents of substrate.

hydroxyl, formation of the tweezer-substrate complex and generation of the ECCD signal.

The C3- and C4- substituted alcohols did however, provide ECCD signals (Table IV.7). These are fairly intense signals and were initially surprising being that the C2-substituted alcohols failed. The success of these alcohols is thought to be the result of moving the hydroxyl binding site away from the pyridine nitrogen binding site. This could relieve congestion at the binding sites and promote formation of the tweezer-substrate complex even with the larger aromatic substituents. If the mnemonics developed for the alkyl substituted pyridinols is applied to the aromatic pyridinols, the ECCD of 1-(4-pyridyl)phenylmethanol (**IV.11**), correlates well; the others do not correlate with the predicted sign. However, for all of the aryl pyridyl alcohols, the (*S*) configuration gave a negative ECCD signal and the (*R*) alcohols produced positive ECCD curves. Frankly, there is no clear reason why the C2- and C3- aryl pyridyl alcohols switch sign. The mnemonic developed places the largest substituent in the least sterically congested location. The large aromatic substituents should also favor this position. Thus, the mnemonic for the alkyl pyridyl alcohols should also be valid for the aryl pyridyl alcohols.

To ensure that the best conditions for ECCD were in use (hexanes at 0 °C), a solvent and temperature study was conducted with (*R*)-(2-pyridyl)mesitylmethanol (**IV.1i**), the results are summarized in Table IV.8. Lowering the temperature to -10 °C in hexanes did improve the signal, but only slightly. Warming to 10 °C or room temperature in hexanes gave no improvement of amplitude. When methylcyclohexane was used the ECCD amplitude was comparable to hexanes. Toluene and CH₂Cl₂ gave no ECCD. Therefore, the initial conditions chosen for suitable for the ECCD study. Furthermore, the sign of the ECCD remained constant under these altered conditions.



(*R*)-IV.1i
60 equiv

Entry	Temp	Solvent	ECCD	Entry	Temp	Solvent	ECCD
1	0 °C	hexanes	427 (+43) 419 (-30) A = +73	5	0 °C	MCH	427 (+53) 416 (-37) A = +90
2	-10 °C	hexanes	426 (+67) 416 (-40) A = +107	6	0 °C	toluene	No ECCD
3	10 °C	hexanes	426 (+43) 419 (-22) A = +65	7	0 °C	CH ₂ Cl ₂	No ECCD
4	rt	hexanes	425 (+31) 417 (-20) A = +51				

Table IV.8: Solvent and temperature screen with (*R*)-IV.1i. 2 μ M tweezer.

In addition to the ECCD study, a UV-Vis analysis of each complex was also conducted yielding Job's plot analysis and for calculation of the tweezer-substrate binding constants. Job's plot analysis revealed the formation of 1:1 complexes (see experimental). The binding constant for the C2-substituted α -alkyl pyridinols exhibited binding constants in the order of 10^5 M^{-1} (Table IV.9). The binding constants for **IV.1f** and **IV.1g** are greater than 10-fold larger than those for **IV.1a** and **IV.1e**. The tighter binding constants help to explain the larger ECCD signals for these substrates. It was hypothesized that moving the hydroxyl center away from the pyridine nitrogen would promote binding with the tweezer by relieving steric congestion

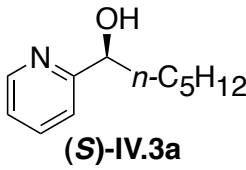
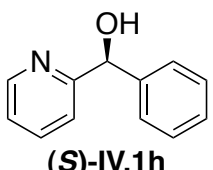
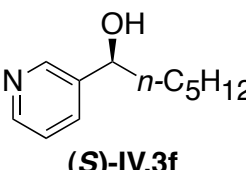
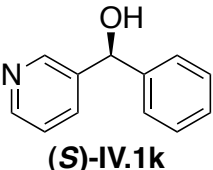
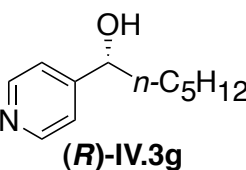
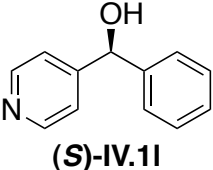
Entry	Substrate	$K_a \pm \text{error (M}^{-1}\text{)}$ R^2	Entry	Substrate	$K_a \pm \text{error (M}^{-1}\text{)}$ R^2
1	 (S)-IV.3a	13224 ± 708 0.99829	4	 (S)-IV.1h	2924 ± 206 0.99681
2	 (S)-IV.3f	4093400 ± 519670 0.99926	5	 (S)-IV.1k	1244200 ± 126100 0.99424
3	 (R)-IV.3g	4494100 ± 1080300 0.99587	6	 (S)-IV.1l	7677400 ± 1333900 0.99926

Table IV.9: Binding constants for C8-Zn-TPFP-Tweezer with pyridyl alcohols. Binding constants for C2-substituted pyridyl alcohols are smaller than the C3- and C4-substituted pyridyl alcohols. This is likely due to steric congestion caused by the binding sites being near to one another. UV-Vis measurements: hexanes, room temperature, 1 μM tweezer. See experimental for UV-Vis titration graph, K_a calculation graph and equation for K_a calculation.

around the binding sites. The increased binding constant for **IV.1f** and **IV.1g** seems to corroborate this hypothesis.

The poor ECCD results for C2-substituted α -aryl pyridinols was thought to be due to increased steric congestion that would inhibit binding with the porphyrin tweezer. Again, the binding constant for **IV.1h** ((2-pyridyl)-phenylmethanol, $K_a = 3,000 \text{ M}^{-1}$) confirms this

hypothesis. At 5-fold smaller than the alkyl substituted alcohols, it would seem that the larger aryl substituent prevents binding with the tweezer. Once again, the K_a values for the C3- and C4-substituted aryl alcohols are larger than the K_a for **IV.1h**. The binding constants for **IV.1k** and **IV.1l** are $1.2 \times 10^6 \text{ M}^{-1}$ and $7.7 \times 10^6 \text{ M}^{-1}$ respectively.

As discussed above, the test substrate (**IV.1a**) provided ECCD with C8-Zn-TPFP-Tz but no ECCD was observed with the tweezers previously used (C3-Zn-TPFP-Tz and C5-Zn-TPFP-Tz). It is hypothesized that this is a consequence of binding to an sp^2 hybridized nitrogen. Unlike the lone pair electrons of a conformationally flexible sp^3 binding group (hydroxyl or amine), the lone pair electrons of the pyridine are in a fixed location and could limit the number of accessible binding modes for the tweezer. Therefore, a longer linker is required to give the tweezer enough conformational flexibility to bind with the conformationally rigid pyridyl alcohol.

To end the ECCD study of chiral pyridyl alcohols, ECCD analysis of *O,O*-dimethylannocherin A (**IV.5**) was conducted. After separation of the enantiomers by chiral HPLC, the absolute configuration was assigned by comparison to the literature reported optical rotation. Finally, each enantiomer was subject to ECCD analysis with C8-Zn-TPFP-Tweezer. Unfortunately, an ECCD signal was not observed, behaving like the other C2- substituted pyridyl aryl methanols.

The chiral pyrrolyl alcohols, (**R**)-**IV.25** and (**S**)-**IV.25**, also provided ECCD with C8-Zn-TPFP-Tz (Table IV.10). The rationale for the observed ECCD sign is summarized in Figure IV.15. It is surprising that these alcohols generate an ECCD signal. For the pyridine based alcohols, there is a lone pair electrons of the pyridine nitrogen that are isolated from the conjugated aromatic

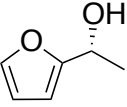
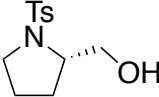
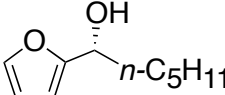
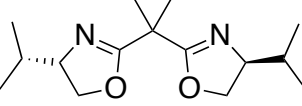
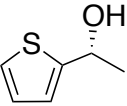
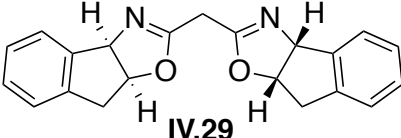
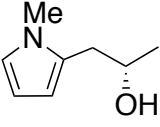
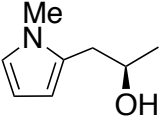
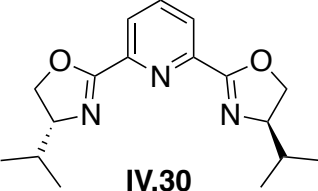
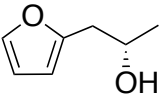
Entry	Chiral Guest	Observed ECCD λ nm ($\Delta\epsilon$)	Entry	Chiral Guest	Observed ECCD λ nm ($\Delta\epsilon$)
1	 (R)-IV.21	No ECCD ^a	7	 IV.27	423 (+238) 413 (-135) A = +373 ^c
2	 (R)-IV.23	No ECCD ^a	8	 IV.28	425 (-75) 415 (+70) A = -145 ^c
3	 (R)-IV.24	No ECCD ^a	9	 IV.29	429 (+2223) 419 (-1408) A = +3631 ^d
4	 (S)-IV.25	423 (-64) 413 (+47) A = -111 ^b			
5	 (R)-IV.25	424 (+77) 413 (-44) A = +121 ^b	10	 IV.30	432 (+309) 425 (-597) 416 (+190) ^d
6	 (S)-IV.26	No ECCD ^a			

Table IV.10: ECCD of other heterocyclic compounds. All measurements: hexanes, 0 °C, 2 μ M C8-Zn-TPFP-Tz tweezer a: Other tweezers used for ECCD analysis were C3-Zn-TPFP-Tz, C5-Zn-TPFP-Tz and C8-Mg-TPFP-Tz. No ECCD was observed. b: 40 equivalents of guest. c: 10 equivalent of guest. d: 1 equivalent of guest.

system. These electrons are thought to be exploited in the binding interaction with the tweezer. For pyrrole, the lone pair electrons of the nitrogen are a part of the conjugated aromatic system. Being that these nitrogen electrons are not isolated from the aromatic system, the pyrrolyl alcohols are expected to exhibit weaker binding with the porphyrin tweezer, weaker than the pyridyl alcohols.

Unfortunately, the furanyl and thiophenyl alcohols did not bind to the tweezer as indicated by UV-Vis analysis as there was no discernible shift of the porphyrin Soret band even in the presence of >1000 equivalents of the alcohol. It has been demonstrated with TPP-Tweezer that enhanced binding affinity with hydroxyl groups can be achieved when the tweezer has been metallated with magnesium rather than with zinc. With this in mind, the C8-Mg-TPFP-Tz was synthesized by subjecting the free-C8-TPFP-Tweezer to magnesium iodide in CH₂Cl₂ for 12 hours. The furanyl and thiophenyl alcohols were then analyzed with C8-Mg-TPFP-Tz. Unfortunately, ECCD was not observed with the C8-Mg-TPFP-Tweezer.

The failure of the furanyl and thiophenyl alcohols is thought to be related to poor substrate binding with the tweezer. Both the oxygen and sulfur of the heteroaromatic rings bear lone pair electrons. It was expected that one porphyrin would bind with the heteroatom and the other porphyrin would bind with the alcohol functionality. As previously discussed, ECCD of chiral hydroxy THFs has been achieved and it is thought that the oxygen of the THF participates in binding with the tweezer. Therefore, it was predicted that the furanyl and thiophenyl alcohols would coordinate in a similar fashion and generate ECCD. Aromaticity is the only difference between the hydroxy THFs and the chiral furyl alcohols so, it is reasoned that the aromatic system withdraws enough electron density from the oxygen to inhibit

coordination with the porphyrin. Therefore, determination of absolute configuration for furanyl and thiophenyl based alcohols cannot be achieved with the current TPFP tweezer.

Finally, ECCD of a few other heterocycle containing molecules was recorded. Three commercially available bisoxazoline ligands and *N*-tosyl-prolinol were evaluated (Table IV.10). All four compounds produced a bisignate curve which indicates that the protected pyrrolidine nitrogen and oxazoline moieties could function as binding sites for the C8-Zn-TPFP-Tweezer. The following figures provide the rationale for the signs of the observed signals for substrates **IV.27**, **IV.28** and **IV.29**. Figure IV.15 provides the most probable binding mode for *N*-tosyl prolinol (**IV.27**). It is thought that there are two possible binding modes, A and B. For A, the tosyl group on the nitrogen is *syn* to and the lone pair electrons of the nitrogen are *anti* to the exocyclic methylene. One porphyrin, P1, coordinates with the lone pair electrons from the same face as the lone pair electrons, *anti* to the exocyclic methylene. This porphyrin will rotate in a counterclockwise direction, away from the five member ring. The second porphyrin, P2, binds with the hydroxyl functionality from the opposite face as P1 as to avoid porphyrin-porphyrin interactions. Once bound, the porphyrin rotates in a clockwise fashion to reduce interaction with the tosyl group. It is assumed that the linker of the porphyrin wraps under the methylenes of the ring as opposed to interacting with the larger tosyl group. Overall, there is a clockwise disposition of the porphyrins and a positive ECCD signal is expected.

The other possible binding mode, Figure IV.14 B, places the lone pair electrons *syn* to the exocyclic methylene. This reduces the steric interactions between the groups of the five member ring by situating the tosyl and the exocyclic methylene *anti* to one another. To bind with the lone pair electrons of the nitrogen, the porphyrin, P2, approaches the prolinol from

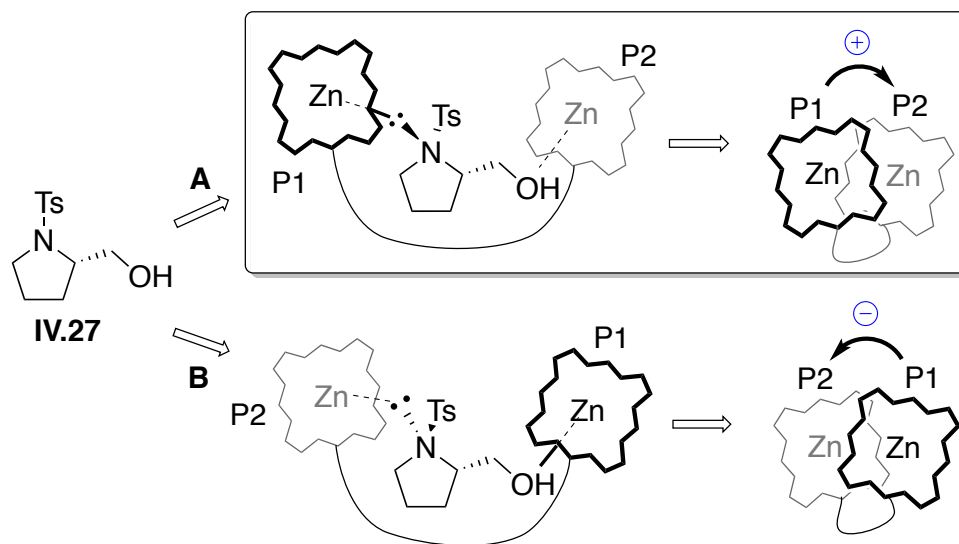


Figure IV.14: Possible binding modes for **IV.27**. See text for explanation. **A:** The binding mode that is thought to be favored in solution. This mode explains the sign of the ECCD signal. **B:** Another possible but unlikely binding mode.

the back face. This porphyrin will rotate in a counterclockwise fashion to minimize interaction with the ring. The other porphyrin, P1, approaches the hydroxyl from the opposite face of the molecule as porphyrin P1 to avoid porphyrin-porphyrin interactions. To bind in this fashion, the hydroxyl which is situated to the back face of the ring, must rotate toward the front face of the ring to be close enough for coordination with the porphyrin. Once bound, the porphyrin will rotate in a clockwise fashion, to reduce interaction with the ring which results in a counterclockwise orientation of the porphyrins and a negative sign is expected. This binding mode is not preferred because of the rotation of the hydroxyl group. Coordination with the rotated hydroxyl group is thought to be unfavorable because there will be greater steric interactions with the ring. Furthermore, this binding mode predicts an ECCD of the opposite

sign than is observed. Therefore, A is thought to be the ECCD active binding mode for this substrate.

Figure IV.15 provides four possible binding modes for the bisoxazole ligand, **IV.28**. To bind with the tweezer, the nitrogens of the oxazolines must be *anti* to one another. This is to avoid porphyrin-porphyrin interactions when the ligand binds. There are two rotomers of the ligand that place the nitrogens in an *anti* relationship. For **IV.28.I**, the isopropyl substituents of the oxazolines are rotated away from the gem-dimethyl unit as opposed to **IV.28.II** where the isopropyl substituents are both rotated toward the gem-dimethyl unit. Steric interaction between the isopropyls and the gem-dimethyl is thought to make this rotomer higher in energy and less favorable.

For these two rotomers there is a total of four possible binding modes with the porphyrin tweezer (Figure IV.15 A - D). In all cases, the porphyrins are expected to bind to the nitrogens of the oxazolines then rotate away from the gem-dimethyl unit. For each rotomer, the tweezer could bind so that the linker wraps under or through the gem-dimethyl moiety. It is thought that there will be higher steric interactions for the linker to wrap through the gem-dimethyl so, B and D are disfavored. Binding mode C is thought to be unfavorable due to the interaction between the isopropyl substituents and the gem-dimethyl unit. Therefore, A is thought to be the preferred binding mode for this bisoxazoline ligand as this model has the fewest unfavorable steric interactions between the ligand and the tweezer. This proposed binding mode predicts a counterclockwise disposition of the porphyrins and a negative ECCD bisignate curve. A negative ECCD signal is observed.

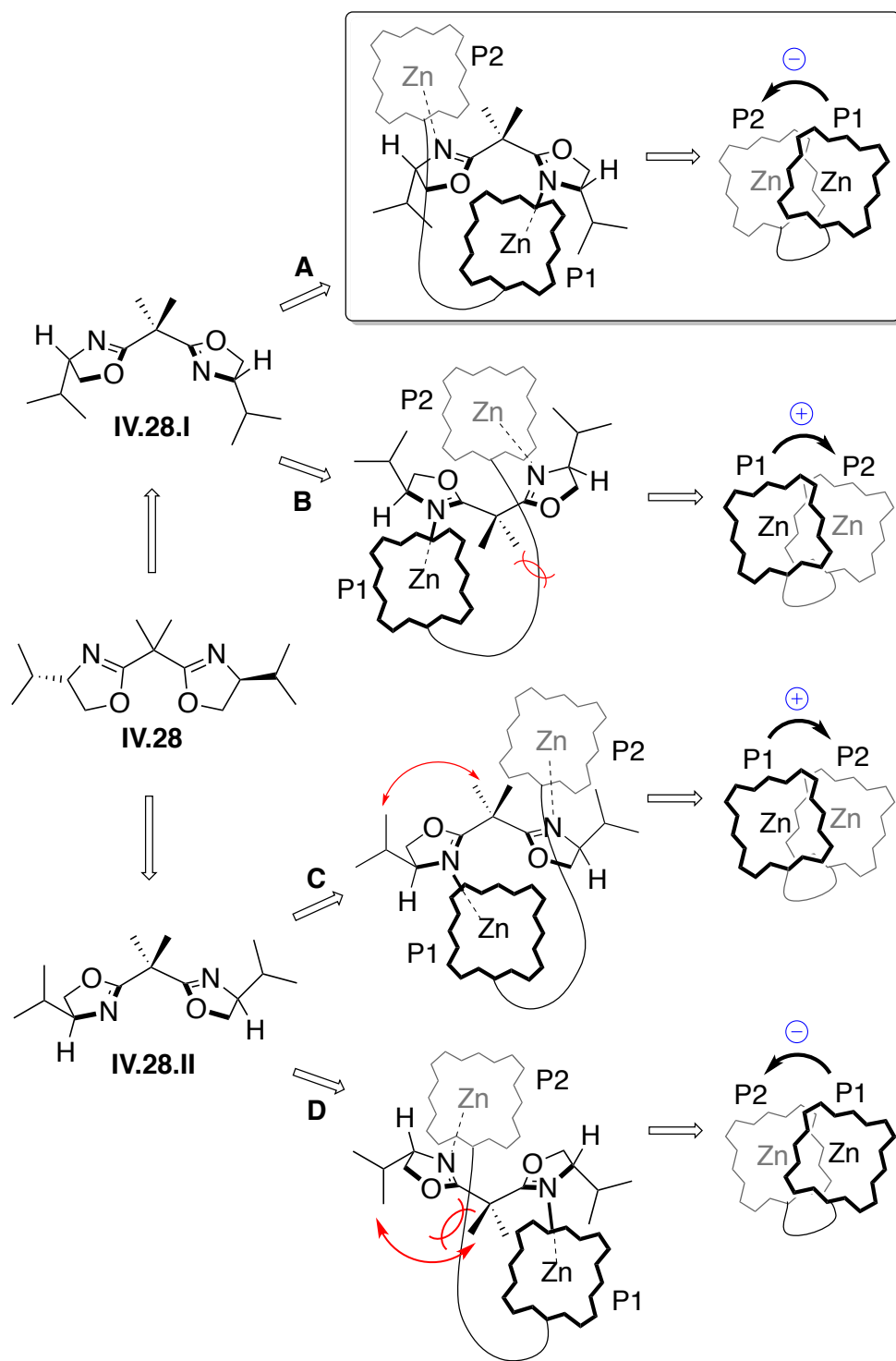


Figure IV.15: Possible binding modes for **IV.28**. There are two possible rotomers **IV.28.I** and **IV.28.II** for a total of four modes (**A - D**). **A** is the preferred model as this has the fewest unfavorable steric interactions. See text for explanation.

The binding model for the bisoxazoline ligand **IV.29** is presented in Figure IV.16. As with the previous system, the nitrogens must be *anti* to one another to bind with the tweezer and avoid porphyrin-porphyrin interactions. Then there are two ways for the tweezer to wrap around the ligand when bound. In Figure IV.16 A, the linker of the tweezer is wrapped around the methylene bridge between the oxazolines. Alternatively, the linker can wrap through the hydrogens of the oxazolines (Figure IV.16 B). The later model is thought to have higher steric interactions between the porphyrins and the oxazolines and as such is the unfavored model. Model A predicts a clockwise orientation of the porphyrins and a positive ECCD signal which matches the sign of the observed signal.

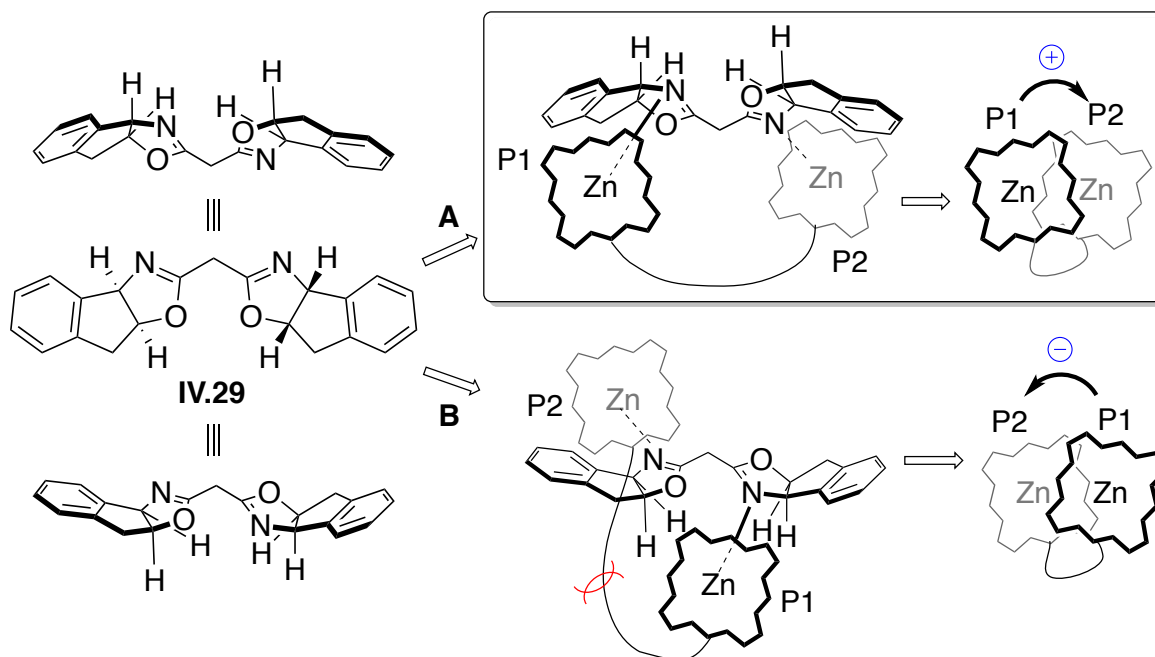


Figure IV.16: Binding models for **IV.29**. There are two possible models, A and B. A is thought to be favored due to minimized steric interactions between the ligand and the tweezer. See text for explanation.

PyBox (**IV.30**) produced a trisignate ECCD curve. This is an indication that multiple ECCD active complexes, at least one complex with a clockwise orientation of the porphyrins and one complex with a counterclockwise orientation of the porphyrins are present in solution. The overlap of these signals would generate the trisignate curve. The multiple ECCD complexes could be a result of competitive binding between the pyridine and oxazoline nitrogens.

At this time, binding models that are specific to each ligand can be proposed. A general mnemonic has not yet been developed. But these results suggest that with a screen of similar substrates an ECCD mnemonic for pyrrolidine and oxazoline containing substrates could be established.

IV.5: Conclusions

Although the ECCD study of heteroaromatic alcohols had varied success, a mnemonic was established for α -alkyl pyridyl alcohols. Unlike the α -aryl pyridyl alcohols, there has not been an ECCD based methodology for the assignment of absolute configuration for α -alkyl pyridyl alcohols previously established. These alcohols provided ECCD signals with as little as 1 equivalent (2 μ mol) of substrate which is considerably less substrate than required for NMR based Mosher ester analysis. Unfortunately, the C2- substituted α -alkyl pyridyl alcohols did not share this success. Yet, C3- and C4-substituted α -alkyl pyridyl alcohols provide intense ECCD signals. Again, disclosure of an ECCD based protocol for the determination of absolute configuration of C3- and C4-substituted α -alkyl pyridyl alcohols has not been previously realized.

UV-Vis titrations of the C8-Zn-TPFP-Tweezer with the pyridyl alcohols elucidated a correlation between binding affinities of the substrate with the substitution pattern of the pyridyl alcohol with C2- substituted pyridyl alcohols exhibiting smaller binding constants than the C3- and C4-substituted α -alkyl pyridyl alcohols. This is thought to be the result of reduced steric congestion about the binding sites.

Finally, the C8-Zn-TPFP-Tweezer was employed for ECCD analysis of other heteroaromatic alcohols with varied success. Selected pyrrole based chiral alcohols provided ECCD signal whereas furan and thiophene based alcohols did not. This is thought to be a result of weak coordination of the furan or thiophene with both zinc and magnesium. ECCD analysis of commercially available chiral bisoxazole ligands was successful.

Future studies could be focused toward extension of the methodology to include α -chiral pyrrolyl alcohols by first finding an efficient way of synthesizing the scaffold. Also, development of a general ECCD based mnemonic for the assignment of absolute configuration for bisoxazole ligands should be pursued.

IV.6: Experimental Procedures

IV.6.1: General Procedures

Where it is stated that dry CH_2Cl_2 or dry toluene was used, the solvent was distilled over CaH_2 . Dry THF and diethyl ether were obtained by distillation from sodium benzophenone ketyl. All other reagents, unless indicated otherwise, were purchased from commercial sources.

Thin layer chromatography was performed on Merck aluminum sheets coated with silica gel (0.2mm thickness). Potassium permanganate, anisaldehyde, polymolybdic acid and UV were used for visualization. Silica chromatography was performed using Dynamic Adsorbents Inc Flash Silica Gel 32-634.

^1H NMR was recorded with Varian Inova 300 or 500 MHz instruments in CDCl_3 . The reported ^1H NMR chemical shifts are relative to the CDCl_3 line (7.24 ppm) and the ^{13}C NMR chemical shifts are relative to the central CDCl_3 line (77.0 ppm). ^{19}F NMR was recorded on the 300 MHz instrument. Mass spectra were recorded using Mass Spectrometry Laboratory using micromass VG-70 mass spectrometer. UV/Vis spectra were recorded on a Perkin-Elmer Lambda 40 spectrophotometer. The CD spectra were recorded on a Jasco J-810 spectropolarimeter equipped with a Neslab 111 temperature controller.

IV.6.2: General Procedure for ECCD Measurement

To hexanes (1 mL) in a 1.0 cm cell, 2 μL of a 1 mM stock solution of zinc porphyrin tweezer (C5-Zn-TPFP-Tz) in anhydrous CH_2Cl_2 was added to provide a 2 μM tweezer solution. The background spectrum was recorded from 380 nm to 450 nm at a scan rate of 50 nm/min at

the specified temperature. Each chiral guest molecule was dissolved in anhydrous CH_2Cl_2 to afford a 1 mM solution then 0.2 to 100 μL of this solution was added to the cell with the tweezer solution affording the host-guest complex. For substrates that required high concentration of guest, a 10 mM solution in anhydrous CH_2Cl_2 was prepared then 1 to 100 μL of this solution was added to the cell with the tweezer solution. The ECCD spectra was immediately recorded following addition of the guest solution (minimum of 4 accumulations). The resultant ECCD spectra, which is reported in millidegrees, was normalized to the tweezer concentration to obtain molecular CD (Mol CD).

IV.6.3: General Procedure for UV-Vis Measurement, Job's Plot Analysis, and Binding Constant Determination

To hexanes (1 mL) in a 1.0 cm cell, 1 μL of a 1 mM stock solution of zinc porphyrin tweezer (C5-Zn-TPFP-Tz) in anhydrous CH_2Cl_2 was added to provide a 1 μM tweezer solution. The background spectrum was recorded from 600 nm to 350 nm at a scan rate of 240 nm/min at room temperature. Each chiral guest molecule was dissolved in anhydrous CH_2Cl_2 to afford a 1 mM solution then 0.2 to 100 μL of this solution was added to the cell with the tweezer solution affording the host-guest complex. For substrates that required high concentration of guest, a 10 mM solution in anhydrous CH_2Cl_2 was prepared then 1 to 100 μL of this solution was added to the cell with the tweezer solution. The UV-Vis spectrum was collected immediately after addition of the guest solution.

The UV-Vis measurements were manipulated for the purpose of determining the complex stoichiometry by Job's plot analysis. First, the molar fraction of tweezer in the solution

was first determined by dividing the moles of tweezer by the total number of moles (moles of tweezer and moles of guest molecule) present in solution. Second, the change in absorbance with each addition of guest molecule was determined. The molar fraction of tweezer and the change of absorbance were multiplied together. The Job's plot was generated by plotting molar fraction tweezer versus molar fraction tweezer multiplied by change in absorbance in Excel. A parabolic curve is generated and the apex of the parabola provides the molar fraction of tweezer in the host-guest complex. A 1:1 complex is formed when the apex falls at a molar fraction of 0.5.

The UV-Vis measurements were manipulated for the purpose of determining the the binding affinity of the guest molecule for the tweezer. The concentration of the guest molecule was determined based on the equivalents of the guest added to the tweezer solution. Also, the change of absorbance for each addition of the guest was determined. Using, KaleidaGraph a plot of the concentration of guest versus the change in absorbance was generated and a line of best fit was calculated based on the following equation:

$$F = F_0 - \frac{1 + (P_T + R_T)K_a - \sqrt{(P_T - R_T)^2 K_a^2 + 2(P_T + R_T)K_a + 1}}{2(P_T K_a)} (F_0 - F_\infty)$$

F = absorbance of the tweezer at a given concentration of guest.

F₀ = absorbance of the tweezer without guest.

F_∞ = absorbance of the tweezer at saturation with the guest.

P_T = concentration of the tweezer.

R_T = concentration of the guest molecule.

K_a = binding constant.

ECCD Spectra for C3-Zn-TPFP-Tz and C5-Zn-TPFP-Tz were recorded by Dr. Xiaoyong Li. The spectra were reported in his thesis.

IV.6.4: Synthesis and Characterization Data for Substrates

IV.6.5: General Procedure for Grignard Additions (**IV.1a-l**)

In a dry 50 mL round bottom flask, magnesium powder and iodine were added to THF. To this suspension, the alkyl bromide was added at the indicated temperature. After 30 minutes, the indicated aldehyde was dissolved in THF then was added dropwise to the magnesium suspension. The reaction was monitored by TLC however, all reactions were complete by 3 hours. The reaction was quenched with NH_4Cl (aq sat, 10 mL) and diluted with H_2O (100 mL). The aqueous layer was extracted with ethyl acetate (3xs, 75 mL) then the organics were combined and dried with brine (1x, 100 mL) and Na_2SO_4 . The solvent was removed under reduced pressure and the crude was purified by column chromatography to provide the desired racemic alcohol.

1-(2-pyridyl)-hexan-1-ol (**IV.1a**): brown oil, 54%

^1H NMR (CDCl_3 , 500 MHz): δ 8.52 (1H, m), 7.65 (1H, dt, J = 1.8, 7.8 Hz), 7.17 (2H, m), 4.70 (1H, m), 4.11 (1H, d, J = 5.7 Hz), 1.80-1.58 (4H, m), 1.42-1.24 (4H, m), 0.85 (3H, t, J = 6.9 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 162.4, 148.1, 136.5, 122.1, 120.3, 72.8, 38.5, 31.8, 24.9, 22.5, 14.0.

Mass Spectrum: $[\text{C}_{11}\text{H}_{18}\text{NO}]^+$ observed 180.1 m/z calculated 180.1 m/z

1-(2-pyridyl)-ethan-1-ol (**IV.1b**): brown oil, 67%

^1H NMR (CDCl_3 , 500 MHz): δ 8.52 (1H, d, J = 5.0 Hz), 7.67 (1H, dt, J = 7.5, 1.5 Hz), 7.26 (1H, dd, J = 7.5, 1.5 Hz), 7.17 (1H, tdd, J = 5.0, 2.0, 0.5 Hz), 4.87 (1H, q, J = 6.5 Hz), 4.21 (1H, br s), 2.01 (1H, m), 1.48 (3H, d, J = 6.5 Hz).

^{13}C NMR (CDCl_3 , 150 MHz): δ 162.98, 147.9, 136.9, 122.2, 119.9, 68.7, 24.2.

Mass Spectrum: $[\text{C}_7\text{H}_{10}\text{NO}]^+$ observed 124.1 m/z calculated 124.1 m/z

1-(2-pyridyl)-2-methylpropan-1-ol (**IV.1c**): brown oil, 99%

^1H NMR (CDCl_3 , 500 MHz): δ 8.52 (1H, td, J = 4.5, 1.0 Hz), 7.64 (1H, dt, J = 8.0, 1.5 Hz), 7.24-7.15 (2H, m), 4.53 (1H, d, J = 4.5 Hz), 4.16 (1H, br s), 2.01 (1H, m), 0.99 (3H, d, J = 7.0 Hz), 0.75 (3H, d, J = 7.0 Hz).

^{13}C NMR (CDCl_3 , 150 MHz): δ 161.3, 147.9, 136.4, 122.2, 121.0, 77.1, 35.1, 19.4, 16.0.

Mass Spectrum: $[\text{C}_9\text{H}_{14}\text{NO}]^+$ observed 152.1 m/z calculated 152.1 m/z

1-(2-pyridyl)-3-methylbutan-1-ol (**IV.1d**): brown oil, 98%

^1H NMR (CDCl_3 , 300 MHz): δ 8.51 (1H, d, J = 4.8 Hz), 7.66 (1H, dt, J = 7.8, 1.5 Hz), 7.25 (1H, d, J = 7.8 Hz), 7.17 (1H, dd, J = 7.5, 2.4 Hz), 4.77 (1H, dd, J = 9.3, 5.1 Hz), 4.36 (1H, br s), 1.90 (1H, m), 1.56 (2H, m), 0.97 (3H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.6 Hz).

^{13}C NMR (CDCl_3 , 150 MHz): δ 163.0, 148.1, 136.6, 122.1, 120.2, 71.3, 47.9, 24.7, 23.5, 21.8.

Mass Spectrum: $[\text{C}_{10}\text{H}_{16}\text{NO}]^+$ observed 166.1 m/z calculated 166.1 m/z

1-(2-pyridyl)-heptadecan-1-ol (**IV.1e**): white solid, 37%

^1H NMR (CDCl_3 , 300 MHz): δ 8.52 (1H, d, J = 5 Hz), 7.71 (1H, dt, J = 7.5, 1.5 Hz), 7.31 (1H, d, J = 7.5 Hz), 7.17 (1H, dd, J = 6.5, 5.5 Hz), 4.75 (1H, dd, J = 7.5, 4.5 Hz), 4.17 (1H, br s), 1.80 (1H, m), 1.69 (1H, m), 1.56 (1H, m), 1.43 - 1.16 (27H, m), 0.86 (3H, t, J = 6.5 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 162.1, 146.7, 138.2, 122.7, 121.1, 72.4, 63.1, 38.4, 32.8, 31.9, 29.70, 29.66, 29.61, 29.60, 29.56, 29.45, 29.35, 25.8, 25.3, 22.7, 14.1.

Mass Spectrum: $[\text{C}_{22}\text{H}_{40}\text{NO}]^+$ observed 334.2 m/z calculated 334.3 m/z

Melting Point: 41 - 43 °C

1-(3-pyridyl)hexan-1-ol (**IV.1f**): brown oil, 17%

^1H NMR (CDCl_3 , 500 MHz): δ 8.46 (1H, s), 8.41 (1H, d, J = 4.5 Hz), 7.67 (1H, d, J = 7.5 Hz), 7.22 (1H, dd, J = 7.5, 4.5 Hz), 4.66 (1H, t, J = 6.5 Hz), 1.80 - 1.63 (4H, m), 1.31 - 1.22 (4H, m), 0.85 (3H, t, J = 7.0 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 148.4, 147.7, 133.7, 123.4, 71.97, 39.1, 31.6, 25.3, 22.5, 13.9.

This sample was taken to the next step without further purification.

Mass Spectrum: $[\text{C}_{11}\text{H}_{18}\text{NO}]^+$ observed 180.1 m/z calculated 180.1 m/z

1-(4-pyridyl)-hexan-1-ol (**IV.1g**): brown oil, 80%

^1H NMR (CDCl_3 , 300 MHz): δ 8.52 (2H, dd, J = 7.5, 1.8 Hz), 7.71 (1H, dt, J = 7.5, 1.5 Hz), 7.31 (1H, d, J = 7.5 Hz), 7.17 (1H, dd, J = 6.5, 5.5 Hz), 4.75 (1H, dd, J = 7.5, 4.5 Hz), 4.17 (1H, br s), 1.80 (1H, m), 1.69 (1H, m), 1.56 (1H, m), 1.43 - 1.16 (27H, m), 0.86 (3H, t, J = 6.5 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 154.7, 149.2, 121.0, 72.65, 38.9, 31.6, 25.1, 22.46, 13.9.

Mass Spectrum: $[\text{C}_{11}\text{H}_{18}\text{NO}]^+$ observed 180.1 m/z calculated 180.1 m/z

(2-pyridyl)phenylmethanol (**IV.1h**): brown solid, 83%

^1H NMR (CDCl_3 , 300 MHz): δ 8.54 (1H, d, J = 3.9 Hz), 7.58 (1H, t, J = 7.5 Hz), 7.36-7.12 (7H, m), 5.74 (1H, s), 5.35 (1H, br s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 160.8, 147.6, 143.1, 137.1, 128.6, 127.8, 127.1, 122.5, 121.5, 74.9.

Mass Spectrum: $[\text{C}_{12}\text{H}_{12}\text{NO}]^+$ observed 186.1 m/z calculated 186.1 m/z

Melting Point: 35 - 40 °C

(2-pyridyl)mesitylmethanol (**IV.1i**): brown solid, 95%

^1H NMR (CDCl_3 , 300 MHz): δ 8.58 (1H, qd, J = 5.1, 0.9 Hz), 7.56 (1H, dt, J = 7.8, 1.8 Hz), 7.18 (1H, tdd, J = 6.0, 5.4, 0.9 Hz), 6.90 (1H, qd, J = 8.1, 1.2 Hz), 6.88 (2H, s), 6.19 (1H, s), 5.38 (1H, br s), 2.26 (3H, s), 2.17 (6H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 161.2, 147.3, 137.5, 137.4, 137.1, 136.7, 134.9, 129.8, 126.8, 121.7, 120.2, 70.3, 21.0, 20.7, 20.2.

Mass Spectrum: $[\text{C}_{15}\text{H}_{18}\text{NO}]^+$ observed 228.1 m/z calculated 228.1 m/z

Melting Point: 42 - 48 °C

(2-pyridyl)tolylmethanol (**IV.1j**): brown semi-solid, 48%

^1H NMR (CDCl_3 , 300 MHz): δ 8.54 (1H, qd, J = 4.8, 0.9 Hz), 7.60 (1H, dt, J = 7.8, 1.8 Hz), 7.26 - 7.11 (6H, m), 5.72 (1H, s), 2.31 (3H, s).

^{13}C NMR (CDCl_3 , 150 MHz): δ 161.1, 147.6, 140.2, 137.4, 136.8, 129.1, 126.9, 122.3, 121.2, 74.8, 21.0.

Mass Spectrum: $[\text{C}_{13}\text{H}_{14}\text{NO}]^+$ observed 200.1 m/z calculated 200.1 m/z

(3-pyridyl)phenylmethanol (**IV.1k**): brown oil, 66%

^1H NMR (CDCl_3 , 300 MHz): δ 8.52 (1H, s), 8.38 (1H, d, J = 3.6 Hz), 7.66 (1H, d, J = 7.8 Hz), 7.36 - 7.11 (6H, m), 5.82 (1H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 148.5, 148.2, 143.2, 134.2, 128.7, 128.4, 127.9, 126.5, 123.4, 73.95.

Mass Spectrum: $[\text{C}_{12}\text{H}_{12}\text{NO}]^+$ observed 186.1 m/z calculated 186.1 m/z

(4-pyridyl)phenylmethanol (**IV.1l**): white solid, 52%

^1H NMR (d^6 -Acetone, 500 MHz): δ 8.42 (1H, td, J = 6.0, 1.5 Hz), 7.34 - 7.21 (7H, m), 5.77 (1H, s).

^{13}C NMR (d^6 -Acetone, 125 MHz): δ 150.4, 129.2, 128.76, 128.67, 128.22, 127.5, 122.0, 74.9.

Mass Spectrum: $[\text{C}_{12}\text{H}_{12}\text{NO}]^+$ observed 186.1 m/z calculated 186.1 m/z

Melting Point: 102 - 105 °C

IV.6.6: General Procedure for MnO_2 Oxidations (**IV.2a-e, h**)

To a 50 mL round bottom flask, the indicated alcohol (50 mg, 0.28 mmol, 1 equiv), manganese dioxide (MnO_2 , 479 mg, 5.57 mmol, 20 equiv) and THF (10 mL) were added and stirred for 12 hours at room temperature. The suspension was filtered through celite, the celite

was rinsed with EtOAc and then solvent was removed under reduced pressure to provide the desired ketone.

1-(2-pyridyl)-hexan-1-one (**IV.2a**): brown oil, 70%

^1H NMR (CDCl_3 , 500 MHz): δ 8.65 (1H, m), 8.01 (1H, td, $J = 1.5, 7.5$ Hz), 7.17 (1H, dt, $J = 2.0, 8.0$ Hz), 7.43 (1H, m), 3.19 (2H, t, $J = 7.5$ Hz), 1.74-1.68 (2H, m), 1.38-1.32 (4H, m), 0.89 (3H, t, $J = 7$ Hz).

Mass Spectrum: $[\text{C}_{11}\text{H}_{16}\text{NO}]^+$ observed 178.1 m/z calculated 178.1 m/z

1-(2-pyridyl)-ethan-1-one (**IV.2b**): brown oil, 67%

^1H NMR (CDCl_3 , 500 MHz): δ 8.66 (1H, d, $J = 4.5$ Hz), 8.01 (1H, d, $J = 7.0$ Hz), 7.80 (1H, dt, $J = 7.5, 2$ Hz), 7.44 (1H, m), 2.70 (3H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 200.1, 153.6, 149.0, 136.8, 127.0, 121.6, 25.7.

Mass Spectrum: $[\text{C}_7\text{H}_8\text{NO}]^+$ observed 122.0 m/z calculated 122.1 m/z

1-(2-pyridyl)-2-methylpropan-1-one (**IV.2c**): brown oil, 37%

^1H NMR (CDCl_3 , 500 MHz): δ 8.66 (1H, d, $J = 4.0$ Hz), 8.02 (1H, d, $J = 8.0$ Hz), 7.81 (1H, dt, $J = 8.0, 1.5$ Hz), 7.43 (1H, ddd, $J = 4.5, 3, 1$ Hz), 4.09 (1H, septet, $J = 6.5$ Hz), 1.90 (6H, d, $J = 7.5$ Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 205.65, 152.9, 148.8, 136.85, 126.8, 122.4, 34.2, 18.6.

Mass Spectrum: $[\text{C}_9\text{H}_{12}\text{NO}]^+$ observed 150.1 m/z calculated 150.1 m/z

1-(2-pyridyl)-3-methylbutan-1-one (**IV.2d**): brown oil, 95%

^1H NMR (CDCl_3 , 500 MHz): δ 8.64 (1H, td, $J = 4, 1$ Hz), 8.01 (1H, dt, $J = 6.5, 1.0$ Hz), 7.08 (2H, dt, $J = 8.0, 1.5$ Hz), 7.43 (1H, ddd, $J = 7.5, 3, 1$ Hz), 3.08 (2H, d, $J = 7.0$ Hz), 2.29 (1H, septet, $J = 6.5$ Hz), 0.97 (6H, d, $J = 6.0$ Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 201.7, 153.8, 148.8, 136.8, 126.8, 121.7, 46.3, 24.7, 22.7.

Mass Spectrum: $[\text{C}_{10}\text{H}_{14}\text{NO}]^+$ observed 164.1 m/z calculated 164.1 m/z

1-(2-pyridyl)-heptadecan-1-one (**IV.2e**): white solid, 95%

^1H NMR (CDCl_3 , 300 MHz): δ 8.64 (1H, td, $J = 5.5, 1.5$ Hz), 8.01 (1H, d, $J = 7.5$ Hz), 7.80 (1H, dt, $J = 8.0, 1.5$ Hz), 7.32 (1H, ddd, $J = 7.5, 4.5, 1.0$ Hz), 3.19 (2H, t, $J = 7.5$ Hz), 1.54 (2H, pentet, $J = 7.0$ Hz), 1.38 - 1.17 (26H, m), 0.86 (3H, t, $J = 8.0$ Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 202.2, 153.6, 148.9, 136.8, 126.9, 121.75, 37.7, 32.8, 31.9, 29.69, 29.65, 29.61, 29.53, 29.49, 29.43, 29.35, 25.7, 24.0, 22.7, 14.1.

Mass Spectrum: $[\text{C}_{22}\text{H}_{38}\text{NO}]^+$ observed 332.2 m/z calculated 332.3 m/z

Melting Point: 31 - 32 °C

(2-pyridyl)phenylmethanone (**IV.2h**): red oil, 84%

^1H NMR (CDCl_3 , 300 MHz): δ 8.71 (1H, ddd, $J = 4.8, 1.8, 0.9$ Hz), 8.06 - 8.01 (3H, m), 7.89 (1H, dt, $J = 7.5, 1.8$ Hz), 7.60 - 7.55 (1H, m), 7.50 - 7.44 (3H, m).

^{13}C NMR (CDCl_3 , 125 MHz): δ 193.8, 155.1, 148.5, 137.0, 136.3, 132.86, 130.95, 128.1, 126.1, 124.6

Mass Spectrum: $[\text{C}_{12}\text{H}_{10}\text{NO}]^+$ observed 184.1 m/z calculated 184.1 m/z

IV.6.7: General Procedure for Noyori Reductions (**IV.3a-e, h**)

1-(pyridin-2-yl)hexanone (**IV.2a**, 50 mg, 0.28 mmol, 1 equiv) and Ru(η^6 -mesitylene)-(*R,R*)-TsDPEN (Noyori's catalyst, 0.25 mol%, too small to measure, a small amount was added) were added to a 5 mL pear shaped flask containing formic acid:triethylamine (2:1 mol:mol, 1 mL) and dichloromethane (0.1 mL). This was stirred for 24 hours under N₂. The reaction was then quenched with H₂O (3 mL) and extracted with ethyl acetate (3xs, 10 mL). The organic layers were combined and washed with NaHCO₃ (aq sat, 2xs, 30 mL) then brine (aq sat, 2xs, 30 mL) and dried with Na₂SO₄. The solvent was removed under reduced pressure and the desired alcohol was isolated via column chromatography.

(*R*)-1-(2-pyridyl)-hexan-1-ol (**(R)-IV.3a**): yellow oil, 54% yield, >99% *ee*

¹H NMR (CDCl₃, 500 MHz): δ 8.52 (1H, m), 7.65 (1H, dt, *J* = 1.8, 7.8 Hz), 7.17 (2H, m), 4.70 (1H, m), 4.11 (1H, d, *J* = 5.7 Hz), 1.80-1.58 (4H, m), 1.42-1.24 (4H, m), 0.85 (3H, t, *J* = 6.9 Hz).

(*R*)-1-(2-pyridyl)-ethan-1-ol (**(R)-IV.3b**): colorless oil, 83% yield, 0% *ee*

¹H NMR (CDCl₃, 500 MHz): δ 8.52 (1H, d, *J* = 5.0 Hz), 7.67 (1H, dt, *J* = 7.5, 1.5 Hz), 7.26 (1H, dd, *J* = 7.5, 1.5 Hz), 7.17 (1H, tdd, *J* = 5.0, 2.0, 0.5 Hz), 4.87 (1H, q, *J* = 6.5 Hz), 4.21 (1H, br s), 2.01 (1H, m), 1.48 (3H, d, *J* = 6.5 Hz).

(*R*)-1-(2-pyridyl)-2-methylpropan-1-ol ((*R*)-**IV.3c**): yellow oil, 76% yield, 0% *ee*

¹H NMR (CDCl₃, 500 MHz): δ 8.52 (1H, td, *J* = 4.5, 1.0 Hz), 7.64 (1H, dt, *J* = 8.0, 1.5 Hz), 7.24-7.15 (2H, m), 4.53 (1H, d, *J* = 4.5 Hz), 4.16 (1H, br s), 2.01 (1H, m), 0.99 (3H, d, *J* = 7.0 Hz), 0.75 (3H, d, *J* = 7.0 Hz).

(*R*)-1-(2-pyridyl)-3-methylbutan-1-ol ((*R*)-**IV.3d**): yellow oil, 65% yield, 0% *ee*

¹H NMR (CDCl₃, 300 MHz): δ 8.51 (1H, d, *J* = 4.8 Hz), 7.66 (1H, dt, *J* = 7.8, 1.5 Hz), 7.25 (1H, d, *J* = 7.8 Hz), 7.17 (1H, dd, *J* = 7.5, 2.4 Hz), 4.77 (1H, dd, *J* = 9.3, 5.1 Hz), 4.36 (1H, br s), 1.90 (1H, m), 1.56 (2H, m), 0.97 (3H, d, *J* = 6.6 Hz), 0.92 (3H, d, *J* = 6.6 Hz).

(*R*)-1-(2-pyridyl)-heptadecan-1-ol ((*R*)-**IV.3e**): white solid, 70% yield, 0% *ee*

¹H NMR (CDCl₃, 300 MHz): δ 8.52 (1H, d, *J* = 5.0 Hz), 7.71 (1H, dt, *J* = 7.5, 1.5 Hz), 7.31 (1H, d, *J* = 7.5 Hz), 7.17 (1H, dd, *J* = 6.5, 5.5 Hz), 4.75 (1H, dd, *J* = 7.5, 4.5 Hz), 4.17 (1H, br s), 1.80 (1H, m), 1.69 (1H, m), 1.56 (1H, m), 1.43 - 1.16 (27H, m), 0.86 (3H, t, *J* = 6.5 Hz).

(*R*)-(2-pyridyl)phenylmethanol ((*R*)-**IV.3h**):

50% conversion after 3 additions of catalyst and 48 hours, 0% *ee*

¹H NMR (CDCl₃, 300 MHz): δ 8.55 (1H, d, *J* = 3.9 Hz), 7.58 (1H, t, *J* = 7.2 Hz), 7.36-7.12 (7H, m), 5.76 (1H, s), 5.33 (1H, br s).

IV.6.8: General Procedure for (S)-MPA Esterification (**IV.4a-I**)

To a 20 mL vial the racemic alcohol (1 equiv), DMAP (1.3 equiv), EDC (1.3 equiv) and (S)-methoxyphenylacetic acid (1.3 equiv) were added. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure and the esters were isolated via gradient column chromatography. The diastereomers were then separated by prep-TLC.

(S)-MPA-1-(2-pyridyl)-hexan-1-ol (**IV.4a**): Yellow oil, 45.5 mg, 99%

^1H NMR (CDCl_3 , 500 MHz): δ 8.52 (1H, d, J = 5.0 Hz), 8.44 (1H, d, J = 4.5 Hz), 7.56 (1H, dt, J = 8.0, 2.0 Hz), 4.65 - 7.29 (11H, m), 7.22 (1H, d, J = 4.0 Hz), 7.13 (1H, dd, J = 7.0, 4.0 Hz), 7.03 (1H, dd, J = 7.5, 4.5 Hz), 6.67 (1H, d, J = 7.5 Hz), 5.83 (1H, dd, J = 8.0, 4.5 Hz), 5.76 (1H, dd, J = 7.5, 5.0 Hz), 4.83 (2H, s), 3.40 (3H, s), 3.36 (3H, s), 1.93 - 1.77 (4H, m), 1.22 (6H, m), 1.09 - 0.98 (6H, m), 0.81 (3H, t, J = 7.0 Hz), 0.73 (3H, t, J = 7.0 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 170.1, 169.81, 159.3, 159.22, 149.2, 148.9, 136.46, 136.3, 136.1, 128.62, 128.48, 127.30, 127.15, 122.54, 122.26, 120.8, 119.8, 82.58, 82.45, 77.17, 77.15, 57.27, 57.21, 34.70, 34.51, 31.32, 31.15, 24.75, 24.48, 22.34, 22.23, 13.84, 13.76.

Mass Spectrum: $[\text{C}_{20}\text{H}_{26}\text{NO}_3]^+$ observed 328.1 m/z calculated 328.2 m/z

(S)-MPA-1*R*-(2-pyridyl)-hexan-1-ol (**(*R,S*)-IV.4a**): Yellow oil, 14 mg, 62%

Diastereomeric Ratio (**(*R,S*)-IV.4a**: **(*S,S*)-IV.4a**): 4:1

^1H NMR (CDCl_3 , 500 MHz): δ 8.54 (1H, dd, J = 4.0, 1.0 Hz), 8.45 (0.25H, d, J = 5.0 Hz), 7.59 (1H, dt, J = 8.0, 1.5 Hz), 7.48 - 7.29 (11H, m), 7.22 (1H, d, J = 4.0 Hz), 7.13 (1H, dd, J = 7.0, 4.0 Hz), 7.03 (1H, dd, J = 7.5, 4.5 Hz), 6.67 (1H, d, J = 7.5 Hz), 5.83 (1H, dd, J = 8.0, 4.5 Hz), 5.76 (1H, dd, J

= 7.5, 5.0 Hz), 4.83 (2H, s), 3.40 (3H, s), 3.36 (3H, s), 1.93 - 1.77 (4H, m), 1.22 (6H, m), 1.09 - 0.98 (6H, m), 0.81 (3H, t, $J = 7.0$ Hz), 0.73 (3H, t, $J = 7.0$ Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 170.06, 169.81, 159.3, 159.22, 149.2, 148.9, 136.46, 136.3, 136.1, 128.62, 128.48, 127.30, 127.15, 122.54, 122.26, 120.8, 119.8, 82.58, 82.45, 77.17, 77.15, 57.27, 57.21, 34.70, 34.51, 31.32, 31.15, 24.75, 24.48, 22.34, 22.23, 13.84, 13.76.

Mass Spectrum: $[\text{C}_{20}\text{H}_{26}\text{NO}_3]^+$ observed 328.1 m/z calculated 328.2 m/z

(*S*)-MPA-1*S*-(2-pyridyl)-hexan-1-ol (**(*R,S*)-IV.4a**): Yellow oil, 22 mg, 98%

Diastereomeric Ratio (**(*R,S*)-IV.4a**: **(*S,S*)-IV.4a**): 0:1

^1H NMR (CDCl_3 , 500 MHz): δ 8.46 (1H, dd, $J = 5.0, 1.0$ Hz), 7.43 - 7.31 (6H, m), 7.05 (1H, ddd, $J = 8.0, 5.0, 1.0$ Hz), 6.68 (1H, d, $J = 7.5$ Hz), 5.84 (1H, dd, $J = 7.5, 5.0$ Hz), 4.84 (1H, s), 3.41 (3H, s), 1.93 - 1.82 (2H, m), 1.22 (4H, m), 0.82 (3H, t, $J = 7.0$ Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 169.9, 159.4, 148.98, 136.36, 136.2, 128.69, 128.54, 127.38, 122.3, 119.9, 82.66, 57.35, 34.77, 31.4, 24.83, 22.4, 13.9.

Mass Spectrum: $[\text{C}_{20}\text{H}_{26}\text{NO}_3]^+$ observed 328.1 m/z calculated 328.2 m/z

(*S*)-MPA-(2-pyridyl)-ethan-1-ol (**IV.4b**): Colorless oil, 32 mg, 74%

^1H NMR (CDCl_3 , 500 MHz): δ 8.54 (1H, d, $J = 5.0$ Hz), 8.47 (1H, d, $J = 6.0$ Hz), 7.62 (1H, t, $J = 7.5$ Hz), 7.47 - 7.30 (11H, m), 7.22 (1H, d, $J = 7.5$ Hz), 7.18 (1H, t, $J = 6.5$ Hz), 7.09 (1H, t, $J = 6.0$ Hz), 6.74 (1H, d, $J = 8.0$ Hz), 5.94 (2H, m), 4.84 (2H, d, $J = 4.0$ Hz), 3.42 (3H, s), 3.39 (3H, s), 1.58 (3H, d, $J = 7.0$ Hz), 1.48 (3H, d, $J = 6.5$ Hz).

^{13}C NMR (CDCl_3 , 150 MHz): δ 169.9, 169.7, 159.7, 159.6, 148.9, 148.7, 136.98, 136.8, 136.1, 128.73, 128.66, 128.57, 128.56, 127.4, 127.1, 122.8, 122.5, 120.5, 119.6, 82.5, 73.6, 73.4, 57.3, 20.6, 20.2.

Mass Spectrum: $[\text{C}_{16}\text{H}_{18}\text{NO}_3]^+$ observed 272.0 m/z calculated 272.1 m/z

(*S*)-MPA-1*R*-(2-pyridyl)-ethan-1-ol (**(*R,S*)-IV.4b**): Colorless oil, 12 mg, 75%

Diastereomeric Ratio (**(*R,S*)-IV.4b**: **(*S,S*)-IV.4b**): 2:1

^1H NMR (CDCl_3 , 500 MHz): δ 8.54 (1H, d, J = 4.0 Hz), 8.47 (0.5H, d, J = 4.0 Hz) 7.62 (1H, dt, J = 7.5, 2.0 Hz), 7.47 - 7.30 (8.5H, m), 7.22 (1H, d, J = 7.5 Hz), 7.18 (1H, dd, J = 6.5, 5.0 Hz), 7.09 (0.5H, dd, J = 6.5, 4.5 Hz), 6.74 (1H, d, J = 8.0 Hz), 5.98 - 5.9 (1.5H, m), 4.84 (1H, s), 4.83 (0.5H, s), 3.42 (1.5H, s), 3.39 (3H, s), 1.58 (1.5H, d, J = 7.0 Hz), 1.47 (1.5H, d, J = 6.5 Hz).

Mass Spectrum: $[\text{C}_{16}\text{H}_{18}\text{NO}_3]^+$ observed 272.0 m/z calculated 272.1 m/z

(*S*)-MPA-1*S*-(2-pyridyl)-ethan-1-ol (**(*S,S*)-IV.4b**): Colorless oil, 9 mg, 56%

Diastereomeric Ratio (**(*R,S*)-IV.4b**: **(*S,S*)-IV.4b**): 1:2

^1H NMR (CDCl_3 , 500 MHz): δ 8.54 (0.5H, d, J = 5.0 Hz), 8.46 (1H, d, J = 4.5 Hz) 7.61 (0.5H, dt, J = 7.5, 2.0 Hz), 7.47 - 7.30 (8.5H, m), 7.22 (0.5H, d, J = 7.5 Hz), 7.18 (0.5H, dd, J = 7.0, 4.5 Hz), 7.09 (1H, dd, J = 8.0, 5.0 Hz), 6.74 (1H, d, J = 8.0 Hz), 5.97 - 5.9 (1.5H, m), 4.84 (0.5H, s), 4.83 (1H, s), 3.42 (3H, s), 3.39 (1.5H, s), 1.57 (3H, d, J = 7.0 Hz), 1.46 (1.5H, d, J = 6.0 Hz).

Mass Spectrum: $[\text{C}_{16}\text{H}_{18}\text{NO}_3]^+$ observed 272.0 m/z calculated 272.1 m/z

(*S*)-MPA-(2-pyridyl)-2-methylpropan-1-ol (**IV.4c**): Yellow oil, 32 mg, 67%

^1H NMR (CDCl_3 , 500 MHz): δ 8.55 (1H, d, J = 5.0 Hz), 8.46 (2H, d, J = 5.0 Hz), 8.01 (1H, d, J = 7.0 Hz), 7.61 (1H, t, J = 6.5 Hz), 7.53 - 7.3 (16H, m), 7.16 (2H, m), 7.06 (2H, dd, J = 7.0, 5.0 Hz), 6.57 (2H, d, J = 8.0 Hz), 5.67 (2H, d, J = 5.0 Hz), 5.54 (1H, d, J = 6.5 Hz), 4.86 (1H, s), 4.85 (2H, s), 3.42 (6H, s), 3.36 (3H, s), 2.34 - 2.23 (3H, m), 0.84 (12H, dd, J = 25.5, 7.5 Hz), 0.65 (3H, dd, J = 7, 2 Hz).

^{13}C NMR (CDCl_3 , 150 MHz): δ 170.1, 169.8, 158.4, 148.6, 136.4, 136.2, 132.9, 129.6, 128.71, 128.69, 128.55, 128.3, 127.4, 127.3, 122.7, 122.4, 121.8, 120.6, 82.6, 81.2, 57.4, 32.43, 32.38, 18.9, 18.7, 17.1, 16.9.

Mass Spectrum: $[\text{C}_{18}\text{H}_{22}\text{NO}_3]^+$ observed 300.0 m/z calculated 300.2 m/z

(*S*)-MPA-1*R*-(2-pyridyl)-2-methylpropan-1-ol (**(*R,S*)-IV.4c**): Yellow oil, 5 mg, 31%

Diastereomeric Ratio (**(*R,S*)-IV.4c**: **(*S,S*)-IV.4c**): 4:1

^1H NMR (CDCl_3 , 500 MHz): δ 8.57 (1H, d, J = 4.0 Hz), 8.46 (0.25H, d, J = 5.0 Hz), 7.63 (1H, t, J = 6.5 Hz), 7.48 - 7.3 (7H, m), 7.2 - 7.16 (2.25H, m), 6.58 (0.25H, d, J = 8.0 Hz), 5.69 (0.25H, d, J = 5.5 Hz), 5.55 (1H, d, J = 6.0 Hz), 4.88 (1H, s), 4.86 (0.25H, s), 3.42 (1H, s), 3.37 (3H, s), 2.33 - 2.23 (1.25H, m), 0.84 (2H, dd, J = 28.5, 7.0 Hz), 0.65 (6H, d, J = 7.0 Hz).

^{13}C NMR (CDCl_3 , 150 MHz): δ 170.1, 136.4, 128.7, 128.6, 127.4, 127.3, 122.8, 121.9, 109.98, 82.5, 57.3, 32.45, 18.7, 17.1.

Mass Spectrum: $[\text{C}_{18}\text{H}_{22}\text{NO}_3]^+$ observed 300.0 m/z calculated 300.2 m/z

(*S*)-MPA-1*S*-(2-pyridyl)-2-methylpropan-1-ol (**(*S,S*)-IV.4c**): Yellow oil, 5 mg, 31%

Diastereomeric Ratio (**(*R,S*)-IV.4c**: **(*S,S*)-IV.4c**): 0:1

^1H NMR (CDCl_3 , 500 MHz): δ 8.46 (1H, d, J = 5.0 Hz), 7.43 - 7.33 (6H, m), 7.10 (1H, t, J = 5.0 Hz), 6.58 (1H, d, J = 8.0 Hz), 5.70 (1H, d, J = 5.5 Hz), 4.86 (1H, s), 3.42 (3H, s), 2.33 (1H, sextet, J = 6.5 Hz), 0.84 (6H, dd, J = 29.5, 7.0 Hz).

^{13}C NMR (CDCl_3 , 150 MHz): δ 169.7, 136.2, 128.7, 128.6, 127.4, 122.5, 120.8, 80.9, 57.4, 32.5, 18.9, 16.9.

Mass Spectrum: $[\text{C}_{18}\text{H}_{22}\text{NO}_3]^+$ observed 300.0 m/z calculated 300.2 m/z

(S)-MPA-(2-pyridyl)-3-methylbutan-1-ol (**IV.4d**): Colorless oil, 28 mg, 56%

^1H NMR (CDCl_3 , 500 MHz): δ 8.55 (1H, d, J = 5.0 Hz), 8.45 (1H, d, J = 4.0 Hz), 8.01 (1H, dd, J = 8.0, 1.5 Hz), 7.60 (1H, dt, J = 7.5, 1.5 Hz), 7.46 - 7.26 (10H, m), 7.19 (1H, d, J = 8.0 Hz), 7.16 (1H, dd, J = 6.5, 5.0 Hz), 7.06 (1H, dd, J = 7.0, 4.5 Hz), 6.67 (1H, d, J = 8.0 Hz), 5.92 (1H, dd, J = 9.0, 4.5 Hz), 5.82 (1H, dd, J = 10.0, 4.5 Hz), 4.84 (1H, s), 4.825 (1H, s), 3.40 (3H, s), 3.36 (3H, s), 1.85 - 1.55 (6H, m), 1.40 - 1.23 (4H, m), 0.91 (6H, dd, J = 7.0, 4.5 Hz), 0.72 (6H, dd, J = 10.0, 7.0 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 170.2, 169.8, 159.6, 159.4, 148.7, 136.86, 136.25, 136.08, 132.9, 129.6, 128.68, 128.53, 128.50, 128.29, 128.13, 127.93, 127.38, 127.23, 122.72, 122.39, 120.98, 119.89, 82.58, 82.50, 75.65, 57.3, 43.84, 43.61, 24.68, 24.33, 23.10, 22.94, 21.80, 21.46.

Mass Spectrum: $[\text{C}_{19}\text{H}_{24}\text{NO}_3]^+$ observed 314.1 m/z calculated 314.2 m/z

(*S*)-MPA-1*R*-(2-pyridyl)-2-methylpropan-1-ol ((*R,S*)-**IV.4d**): Yellow oil, 8 mg, 57%

Diastereomeric Ratio ((*R,S*)-**IV.4d**: (*S,S*)-**IV.4d**): 1:0

¹H NMR (CDCl₃, 500 MHz): δ 8.58 (1H, d, *J* = 4.5 Hz), 7.65 (1H, m), 7.46 (2H, dd, *J* = 7.5, 2.0 Hz), 7.34 - 7.30 (4H, m), 7.22 (1H, d, *J* = 7.5 Hz), 5.83 (1H, dd, *J* = 10.0, 4.0 Hz), 4.87 (1H, s), 3.37 (3H, s), 1.82 (1H, m), 1.59 (1H, m), 1.27 (1H, m), 0.72 (6H, dd, *J* = 16.0, 7.0 Hz).

¹³C NMR (CDCl₃, 125 MHz): δ 170.2, 159.2, 136.2, 128.72, 128.55, 127.26, 122.92, 122.49, 121.2, 82.5, 75.3, 57.3, 43.7, 24.4, 22.96, 21.44.

Mass Spectrum: [C₁₉H₂₄NO₃]⁺ observed 314.1 m/z calculated 314.2 m/z

(*S*)-MPA-1*S*-(2-pyridyl)-2-methylpropan-1-ol ((*S,S*)-**IV.4d**): Yellow oil, 9 mg, 64%

Diastereomeric Ratio ((*R,S*)-**IV.4d**: (*S,S*)-**IV.4d**): 0:1

¹H NMR (CDCl₃, 500 MHz): δ 8.47 (1H, d, *J* = 4.5 Hz), 8.01 (1H, d, *J* = 7.0 Hz), 7.43 - 7.31 (5H, m), 7.09 (1H, dd, *J* = 7.0, 5.5 Hz), 6.68 (1H, d, *J* = 7.5 Hz), 5.92 (1H, dd, *J* = 9.5, 4.5 Hz), 4.83 (1H, s), 3.40 (3H, s), 1.85 - 1.60 (3H, m), 0.91 (6H, t, *J* = 6.5 Hz).

¹³C NMR (CDCl₃, 125 MHz): δ 169.8, 136.04, 132.9, 129.6, 128.73, 128.56, 128.30, 127.40, 122.58, 120.1, 82.55, 75.4, 57.3, 43.84, 24.71, 23.10, 21.8.

Mass Spectrum: [C₁₉H₂₄NO₃]⁺ observed 314.1 m/z calculated 314.2 m/z

(*S*)-MPA-(2-pyridyl)-heptadecan-1-ol (**IV.4e**): White solid, 83 mg, 77%

¹H NMR (CDCl₃, 500 MHz): δ 8.525 (1H, d, *J* = 5.0 Hz), 8.43 (1H, dd, *J* = 5.0, 1.0 Hz), 7.57 (1H, dt, *J* = 7.5, 1.5 Hz), 7.47 - 7.28 (12H, m), 7.18 (1H, d, *J* = 7.5 Hz), 7.13 (1H, ddd, *J* = 7.0, 4.5, 1.0 Hz), 7.03 (1H, ddd, *J* = 7.5, 5.0, 1.0 Hz), 6.67 (1H, d, *J* = 7.5 Hz), 5.83 (1H, dd, *J* = 8.5, 5.0 Hz), 5.75 (1H,

dd, $J = 7.5, 5.0$ Hz), 4.831 (1H, s), 4.828 (1H, s), 3.40 (3H, s), 3.36 (3H, s), 1.92 - 1.77 (6H, m), 1.28 - 0.95 (52H, m), 0.84 (6H, t, $J = 7.0$ Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 170.1, 169.8, 159.4, 159.3, 149.2, 148.95, 136.49, 136.34, 136.31, 136.16, 128.65, 128.51, 127.34, 127.20, 122.6, 122.3, 120.8, 119.8, 82.63, 82.49, 77.21, 77.18, 57.29, 57.24, 34.8, 34.6, 31.9, 29.65, 29.60, 29.57, 29.47, 29.38, 29.31, 29.29, 29.22, 29.05, 25.1, 24.9, 22.6, 14.1.

Mass Spectrum: $[\text{C}_{31}\text{H}_{48}\text{NO}_3]^+$ observed 482.2 m/z calculated 482.4 m/z

Melting Point: 29 - 30 °C

(*S*)-MPA-1*R*-(2-pyridyl)-heptadecan-1-ol (**(*R,S*)-IV.4e**): White solid, 33 mg, 80%

Diastereomeric Ratio (**(*R,S*)-IV.4e**: **(*S,S*)-IV.4e**): 2:1

^1H NMR (CDCl_3 , 500 MHz): δ 8.53 (1H, d, $J = 5.0$ Hz), 8.45 (0.5H, $J = 5.0$ Hz), 7.59 (1H, dt, $J = 7.5, 1.5$ Hz), 7.47 - 7.29 (8H, m), 7.18 (1H, d, $J = 7.5$ Hz), 7.14 (1H, dd, $J = 7.5, 6.0$ Hz), 7.05 (0.5H, dd, $J = 7.5, 6.0$ Hz), 6.67 (0.1H, d, $J = 7.5$ Hz), 5.84 (0.5H, dd, $J = 7.5, 4.5$ Hz), 5.75 (1H, dd, $J = 7.5, 6.0$ Hz), 4.84 (1.5H, s), 3.41 (1.5H, s), 3.37 (3H, s), 1.92 - 1.77 (3H, m), 1.28 - 0.95 (42H, m), 0.856 (4.5H, t, $J = 7.0$ Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 170.1, 159.3, 149.3, 148.98, 136.52, 136.35, 128.68, 128.54, 127.37, 127.22, 122.6, 122.3, 120.9, 119.9, 82.65, 82.5, 57.33, 57.28, 34.8, 34.6, 31.9, 29.67, 29.63, 29.58, 29.41, 29.33, 29.31, 29.24, 29.07, 24.9, 22.7, 14.1.

Mass Spectrum: $[\text{C}_{31}\text{H}_{48}\text{NO}_3]^+$ observed 482.2 m/z calculated 482.4 m/z

Melting Point: 30 - 34 °C

(S)-MPA-15-(2-pyridyl)-heptadecan-1-ol ((**S,S**)-**IV.4e**): Colorless oil, 40 mg, 98%

Diastereomeric Ratio ((**R,S**)-**IV.4e**: (**S,S**)-**IV.4e**): 0:1

^1H NMR (CDCl_3 , 500 MHz): δ 8.46 (1H, dd, $J = 5.0, 1.0$ Hz), 7.43 - 7.31 (6H, m), 7.05 (1H, dd, $J = 7.5, 5.0$ Hz), 6.68 (1H, d, $J = 7.5$ Hz), 5.84 (1H, dd, $J = 8.0, 5.0$ Hz), 4.83 (1H, s), 3.42 (3H, s), 1.92 - 1.85 (2H, m), 1.23 (28H, m), 0.86 (3H, t, $J = 6.5$ Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 169.9, 159.4, 148.99, 136.35, 136.18, 128.69, 128.54, 127.38, 122.3, 119.9, 82.66, 57.35, 34.8, 31.9, 29.68, 29.64, 29.60, 29.50, 29.41, 29.34, 29.24, 25.2, 22.66, 14.1.

Mass Spectrum: $[\text{C}_{31}\text{H}_{48}\text{NO}_3]^+$ observed 482.2 m/z calculated 482.4 m/z

Melting Point: 28 - 31 °C

(S)-MPA-(3-pyridyl)-hexan-1-ol (**IV.4f**): Yellow oil, 17 mg, 47%

^1H NMR (CDCl_3 , 500 MHz): δ 8.53 (1H, d, $J = 1.5$ Hz), 8.50 (1H, d, $J = 5.0$ Hz), 8.42 (1H, dd, $J = 5.0, 1.5$ Hz), 8.31 (1H, d, $J = 2.0$ Hz), 7.54 (1H, dt, $J = 7.5, 1.5$ Hz), 7.43 - 7.28 (10H, m), 7.23 - 7.19 (2H, m), 7.05 (1H, dd, $J = 7.5, 5$ Hz), 5.74 (2H, m), 4.77 (1H, s), 4.74 (1H, s), 3.37 (3H, s), 3.35 (3H, s), 1.90 - 1.5 (4H, m), 1.38 - 0.80 (15H, m), 0.74 (3H, t, $J = 7.5$ Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 169.94, 169.78, 149.32, 149.10, 148.20, 147.93, 136.16, 135.87, 135.78, 135.61, 134.03, 133.54, 128.80, 128.77, 128.60, 127.20, 127.14, 123.29, 123.11, 82.6, 74.54, 74.53, 57.3, 35.99, 35.76, 31.27, 31.13, 24.83, 24.54, 22.37, 22.28, 13.86, 13.79.

Mass Spectrum: $[\text{C}_{20}\text{H}_{26}\text{NO}_3]^+$ observed 328.1 m/z calculated 328.2 m/z

(*S*)-MPA-1*R*-(3-pyridyl)-hexan-1-ol ((*R,S*)-**IV.4f**): Colorless oil, 6 mg, 71%

Diastereomeric Ratio ((*R,S*)-**IV.4f**: (*S,S*)-**IV.4f**): 20:1

¹H NMR (CDCl₃, 500 MHz): δ 8.55 (1H, s), 8.51 (1H, s), 8.43 (0.05H, s), 8.33 (0.05H, s), 7.55 (1H, d, *J* = 7.5 Hz), 7.43 - 7.21 (6H, m), 5.75 (1H, t, *J* = 6.0 Hz), 4.75 (1H, s), 3.36 (3H, s), 1.80 - 1.6 (2H, m), 1.23 - 0.80 (6H, m), 0.75 (3H, t, *J* = 6.0 Hz).

¹³C NMR (CDCl₃, 125 MHz): δ 169.95, 149.31, 148.18, 136.17, 134.13, 128.80, 128.63, 127.16, 123.34, 82.6, 74.54, 57.3, 35.77, 31.15, 24.57, 22.3, 13.83.

Mass Spectrum: [C₂₀H₂₆NO₃]⁺ observed 328.1 m/z calculated 328.2 m/z

(*S*)-MPA-1*S*-(3-pyridyl)-hexan-1-ol ((*S,S*)-**IV.4f**): Colorless oil, 9 mg, quantitative yield

Diastereomeric Ratio ((*R,S*)-**IV.4f**: (*S,S*)-**IV.4f**): 0:1

¹H NMR (CDCl₃, 500 MHz): δ 8.43 (1H, dd, *J* = 5.5 Hz), 8.32 (1H, s), 8.54 (1H, dt, *J* = 7.5, 1.5 Hz), 7.45 - 7.22 (6H, m), 7.06 (1H, dd, *J* = 7.5, 5.0 Hz), 5.75 (1H, t, *J* = 7.0 Hz), 4.78 (1H, s), 3.37 (3H, s), 1.90 - 1.5 (2H, m), 1.38 - 0.80 (7H, m).

¹³C NMR (CDCl₃, 125 MHz): δ 169.95, 149.3, 148.2, 136.19, 134.12, 128.8, 128.62, 127.17, 123.32, 82.6, 74.54, 57.3, 35.8, 31.15, 24.57, 22.3, 13.81.

Mass Spectrum: [C₂₀H₂₆NO₃]⁺ observed 328.1 m/z calculated 328.2 m/z

(*S*)-MPA-(4-pyridyl)-hexan-1-ol (**IV.4g**): Yellow oil, 40 mg, 89%

¹H NMR (CDCl₃, 500 MHz): δ 8.49 (2H, d, *J* = 6.0 Hz), 8.33 (2H, d, *J* = 6.0 Hz), 7.41 - 7.26 (H, m), 7.10 (2H, d, *J* = 5.5 Hz), 6.77 (2H, d, *J* = 6.0 Hz), 5.67 (2H, m), 4.79 (1H, s), 4.77 (1H, s), 3.37 (3H, s), 3.36 (3H, s), 1.8 - 1.56 (6H, m), 1.35 - 0.71 (16H, m).

^{13}C NMR (CDCl_3 , 125 MHz): δ 169.9, 169.7, 155.9, 149.92, 149.70, 149.52, 149.12, 149.03, 136.1, 135.9, 128.89, 128.81, 128.66, 128.62, 128.29, 127.4, 127.1, 121.01, 120.90, 120.69, 120.56, 82.54, 82.45, 74.96, 74.93, 57.29, 57.21, 42.6, 35.77, 35.64, 32.02, 31.22, 31.07, 24.6, 24.3, 22.39, 22.29, 22.19, 13.87, 13.81, 13.74.

Mass Spectrum: $[\text{C}_{20}\text{H}_{26}\text{NO}_3]^+$ observed 328.1 m/z calculated 328.2 m/z

(S)-MPA-1*R*-(4-pyridyl)-hexan-1-ol ((*R,S*)-IV.4g): Colorless oil, 9 mg, 45%

Diastereomeric Ratio ((*R,S*)-IV.4g: (*S,S*)-IV.4g): 4:1

^1H NMR (CDCl_3 , 500 MHz): δ 8.51 (2H, d, J = 5.5 Hz), 8.36 (0.5H, d, J = 5.5 Hz), 7.44 - 7.23 (6.25H, m), 7.11 (2H, d, J = 6.0 Hz), 6.79 (0.5H, d, J = 6.0 Hz), 5.69 (1.25H, m), 4.81 (0.25H, s), 4.79 (1H, s), 3.39 (0.75H, s), 3.38 (3H, s), 1.75 - 1.58 (2.5H, m), 1.23 - 0.73 (12H, m).

^{13}C NMR (CDCl_3 , 125 MHz): δ 169.9, 149.95, 149.7, 149.14, 136.1, 128.84, 128.68, 128.65, 127.4, 127.1, 120.9, 82.6, 75.05, 57.37, 35.771, 31.14, 24.38, 22.27, 13.81.

Mass Spectrum: $[\text{C}_{20}\text{H}_{26}\text{NO}_3]^+$ observed 328.1 m/z calculated 328.2 m/z

(S)-MPA-1*S*-(4-pyridyl)-hexan-1-ol ((*S,S*)-IV.4g): Colorless oil, 10 mg, 50%

Diastereomeric Ratio ((*R,S*)-IV.4g: (*S,S*)-IV.4g): 0:1

^1H NMR (CDCl_3 , 500 MHz): δ 8.36 (2H, d, J = 5.5 Hz), 7.38 - 7.33 (5H, m), 6.79 (2H, d, J = 6.0 Hz), 5.69 (1H, dd, J = 8.0, 6.0 Hz), 4.81 (1H, s), 3.39 (3H, s), 1.8 - 1.56 (2H, m), 1.22 (4H, m), 0.83 (3H, t, J = 7.5 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 169.7, 150.95, 149.74, 149.05, 135.9, 128.93, 128.69, 127.37, 121.03, 120.58, 82.53, 75.02, 57.29, 35.86, 31.3, 24.7, 22.37, 13.88.

Mass Spectrum: $[\text{C}_{20}\text{H}_{26}\text{NO}_3]^+$ observed 328.1 m/z calculated 328.2 m/z

(*S*)-MPA-(2-pyridyl)phenylmethanol (**IV.4h**): White solid, 43 mg, 96%

^1H NMR (CDCl_3 , 500 MHz): δ 8.53 (1H, d, J = 5.0 Hz), 8.44 (1H, dd, J = 5.0, 1.0 Hz), 7.59 (1H, dt, J = 8.0, 1.5 Hz), 7.48 - 7.11 (23H, m), 7.04 (1H, dd, J = 7.5, 5.0 Hz), 6.90 (1H, s), 6.87 (1H, s), 6.80 (1H, d, J = 7.5 Hz), 4.93 (1H, s), 4.91 (1H, s), 3.41 (3H, s), 3.41 (3H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 169.40, 169.26, 158.74, 158.70, 149.36, 149.19, 138.54, 138.39, 136.68, 136.51, 136.07, 135.99, 128.75, 128.68, 128.58, 128.54, 128.48, 128.29, 128.19, 127.92, 127.43, 127.34, 127.30, 126.77, 122.68, 122.41, 120.9, 119.6, 82.57, 82.53, 78.36, 78.28, 57.38.

Mass Spectrum: $[\text{C}_{24}\text{H}_{26}\text{NO}_3]^+$ observed 334.0 m/z calculated 334.1 m/z

Melting Point: 62 - 68 °C

(*R,S*)-MPA-(2-pyridyl)phenylmethanol (**(*R,S*)-IV.4h**): White solid, 14 mg, 65%

Diastereomeric Ratio (**(*R,S*)-IV.4h**: **(*S,S*)-IV.4h**): 10:1

^1H NMR (CDCl_3 , 500 MHz): δ 8.54 (1H, d, J = 4.0 Hz), 8.44 (0.1H, d, J = 5.0 Hz), 7.61 (1H, t, J = 8.0 Hz), 7.48 - 7.11 (12H, m), 6.86 (1H, s), 4.93 (1H, s), 4.91 (0.1H, s), 3.41 (3H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 169.40, 169.26, 158.74, 158.70, 149.36, 149.19, 138.54, 138.39, 136.68, 136.51, 136.07, 135.99, 128.75, 128.68, 128.58, 128.54, 128.48, 128.29, 128.19, 127.92, 127.43, 127.34, 127.30, 126.77, 122.68, 122.41, 120.9, 119.6, 82.57, 82.53, 78.36, 78.28, 57.38.

Mass Spectrum: $[\text{C}_{24}\text{H}_{26}\text{NO}_3]^+$ observed 334.0 m/z calculated 334.1 m/z

Melting Point: 60 - 65 °C

(*S,S*)-MPA-(2-pyridyl)phenylmethanol (**(*S,S*)-IV.4h**): Colorless oil, 17 mg, 79%

Diastereomeric Ratio (**(*R,S*)-IV.4h**: **(*S,S*)-IV.4h**): 0:1

Single Diastereomer

^1H NMR (CDCl_3 , 500 MHz): δ 8.44 (1H, d, J = 5.0 Hz), 7.47 - 7.24 (11H, m), 7.06 (1H, dd, J = 7.0, 4.5 Hz), 6.89 (1H, s), 4.90 (1H, s), 3.42 (3H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 169.30, 158.78, 149.24, 138.56, 136.55, 136.10, 128.79, 128.62, 128.52, 128.24, 127.48, 127.39, 122.44, 119.7, 82.58, 78.32, 57.43.

Mass Spectrum: $[\text{C}_{24}\text{H}_{26}\text{NO}_3]^+$ observed 334.0 m/z calculated 334.1 m/z

These diastereomers sufficiently separated by column chromatography therefore, prep TLC was not utilized for separation.

(*R,S*)-MPA-(2-pyridyl)mesitylmethanol (**(*R,S*)-IV.4i**): Colorless oil, 22 mg, quantitative yield

Diastereomeric Ratio (**(*R,S*)-IV.4i**: **(*S,S*)-IV.4i**): 3:1

^1H NMR (CDCl_3 , 500 MHz): δ 8.51 (1H, d, J = 5.0 Hz), 8.37 (0.3H, d, J = 5.0 Hz), 7.53 (2.25H, m), 7.43 - 7.25 (8H, m), 7.12 (1H, d, J = 8.0 Hz), 7.09 (1H, dd, J = 7.5, 3.5 Hz), 6.99 (0.3H, dd, J = 8.0, 5.0 Hz), 6.89 (0.3H, d, J = 7.5 Hz), 6.82 (1.6H, s), 6.73 (2H, s), 6.54 (0.3H, d, J = 8.5 Hz), 4.95 (1H, s), 4.87 (0.3H, s), 3.43 (3H, s), 3.42 (0.9H, s), 2.25 - 2.12 (12H, m).

^{13}C NMR (CDCl_3 , 125 MHz): δ 169.99, 169.7, 159.0, 158.7, 149.35, 149.22, 137.82, 137.73, 136.1, 135.9, 131.9, 129.95, 129.77, 129.60, 128.81, 128.67, 128.61, 128.52, 127.59, 127.42, 121.8, 121.5, 120.1, 119.5, 82.9, 82.5, 74.3, 73.7, 57.49, 57.41, 20.91, 20.46, 20.34, 20.19.

Mass Spectrum: $[\text{C}_{24}\text{H}_{26}\text{NO}_3]^+$ observed 376.0 m/z calculated 376.2 m/z

These diastereomers sufficiently separated by column chromatography therefore, prep TLC was not utilized for separation.

(*S,S*)-MPA-(2-pyridyl)mesitylmethanol (**(*S,S*)-IV.4i**): Colorless oil, 220 mg, 91%

Diastereomeric Ratio (**(*R,S*)-IV.4i**: **(*S,S*)-IV.4i**): 0:1

¹H NMR (CDCl₃, 500 MHz): δ 8.37 (1H, d, *J* = 5.0 Hz), 7.6 - 7.3 (6H, m), 6.99 (1H, dd, *J* = 8.0, 5.0 Hz), 6.83 (1H, s), 6.54 (1H, d, *J* = 7.5 Hz), 4.87 (1H, s), 3.42 (3H, s), 2.25 (3H, s), 2.23 (6H, s).

¹³C NMR (CDCl₃, 125 MHz): δ 169.7, 159.0, 149.2, 138.1, 137.8, 136.5, 135.8, 132.4, 129.8, 128.81, 128.67, 127.6, 121.5, 119.5, 82.5, 73.7, 57.4, 20.94, 20.46.

Mass Spectrum: [C₂₄H₂₆NO₃]⁺ observed 376.0 m/z calculated 376.2 m/z

These diastereomers sufficiently separated by column chromatography therefore, prep TLC was not utilized for separation.

(*R,S*)-MPA-(2-pyridyl)tolylmethanol (**(*R,S*)-IV.4j**): Colorless oil, 22 mg, quantitative yield

Diastereomeric Ratio (**(*R,S*)-IV.4j**: **(*S,S*)-IV.4j**): 10:1

¹H NMR (CDCl₃, 500 MHz): δ 8.53 (1H, dd, *J* = 4.0, 1.0 Hz), 8.43 (0.1H, d, *J* = 4.0 Hz), 7.60 (1H, dt, *J* = 7.5, 1.5 Hz), 7.47 - 7.32 (6H, m), 7.26 (1H, d, *J* = 7.5 Hz), 7.21 (0.2H, d, *J* = 8.5 Hz), 7.13 (1H, ddd, *J* = 7.0, 5.0, 1.0 Hz), 7.00 (4H, dd, *J* = 7.5, 4.5 Hz), 6.82 (1H, s), 4.91 (1H, s), 4.88 (0.1H, s), 3.41 (3H, s), 2.24 (3H, s).

¹³C NMR (CDCl₃, 125 MHz): δ 169.2, 158.95, 149.2, 138.1, 136.5, 136.2, 135.6, 129.2, 128.77, 128.61, 127.5, 127.4, 122.4, 119.6, 82.6, 78.2, 57.4, 21.1.

Mass Spectrum: [C₂₂H₂₂NO₃]⁺ observed 348.0 m/z calculated 348.2 m/z

(*S,S*)-MPA-(2-pyridyl)tolylmethanol (**(*S,S*)-IV.4j**): Yellow oil, 22 mg, quantitative yield

Diastereomeric Ratio (**(*R,S*)-IV.4j**: **(*S,S*)-IV.4j**): 1:20

^1H NMR (CDCl_3 , 500 MHz): δ 8.53 (0.05H, d), 8.43 (1H, dd, $J = 5.0, 1.0$ Hz), 7.6 (0.05H, t), 7.47 - 7.28 (6H, m), 7.21 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 7.5$ Hz), 7.04 (1H, dd, $J = 7.5, 4.5$ Hz), 6.86 (1H, s), 6.77 (1H, d, $J = 8.0$ Hz), 4.88 (1H, s), 3.41 (3H, s), 2.28 (3H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 169.5, 158.9, 149.4, 137.7, 136.7, 136.1, 135.5, 129.0, 128.67, 128.56, 127.3, 126.8, 122.6, 120.8, 82.6, 78.4, 57.4, 21.1.

Mass Spectrum: $[\text{C}_{22}\text{H}_{22}\text{NO}_3]^+$ observed 348.0 m/z calculated 348.2 m/z

(*S*)-MPA-(3-pyridyl)phenylmethanol (**IV.4k**): Yellow oil, 61 mg, 60%

^1H NMR (CDCl_3 , 500 MHz): δ 8.55 (1H, s), 8.51 (1H, d, $J = 3.5$ Hz), 8.42 (1H, d, $J = 3.5$ Hz), 8.295 (1H, s), 7.52 (1H, d, $J = 8.5$ Hz), 7.40 - 7.15 (H, m), 7.07 (1H, dd, $J = 8.0, 5.0$ Hz), 6.99 - 6.97 (3H, m), 6.88 (1H, s), 6.87 (1H, s), 4.86 (2H, s), 3.382 (3H, s), 3.378 (3H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 169.4, 149.1, 148.77, 148.45, 147.9, 138.5, 138.33, 135.78, 135.56, 135.4, 135.1, 134.4, 128.97, 128.87, 128.74, 128.67, 128.57, 128.53, 128.18, 127.3, 127.28, 127.15, 126.5, 123.4, 123.2, 82.60, 82.53, 75.3, 57.38, 57.35.

Mass Spectrum: $[\text{C}_{24}\text{H}_{26}\text{NO}_3]^+$ observed 334.0 m/z calculated 334.1 m/z

(*R,S*)-MPA-(3-pyridyl)phenylmethanol (**(*R,S*)-IV.4k**): Colorless oil, 30 mg, quantitative yield

Diastereomeric Ratio (**(*R,S*)-IV.4k**: **(*S,S*)-IV.4k**): 10:1

¹H NMR (CDCl₃, 500 MHz): δ 8.55 (1H, s), 8.51 (1H, d, *J* = 4.0 Hz), 8.43 (0.1H, d, *J* = 3.5 Hz), 8.3 (0.1H, s), 7.52 (1H, d, *J* = 7.5 Hz), 7.40 - 7.15 (9H, m), 7.06 (0.1H, dd, *J* = 8.5, 4.5 Hz), 6.98 (2H, d, *J* = 6.5), 6.87 (1H, s), 4.86 (1H, s), 3.38 (3H, s).

¹³C NMR (CDCl₃, 125 MHz): δ 169.4, 149.4, 149.1, 148.74, 138.4, 135.8, 135.4, 134.9, 134.1, 128.97, 128.87, 128.74, 128.69, 128.54, 128.16, 127.3, 127.17, 126.5, 123.4, 82.60, 75.4, 57.4.

Mass Spectrum: [C₂₄H₂₆NO₃]⁺ observed 334.0 m/z calculated 334.1 m/z

(*S,S*)-MPA-(3-pyridyl)phenylmethanol (**(*S,S*)-IV.4k**): Yellow oil, 30 mg, quantitative yield

Diastereomeric Ratio (**(*R,S*)-IV.4k**: **(*S,S*)-IV.4k**): 1:20

¹H NMR (CDCl₃, 500 MHz): δ 8.63 (0.05H, s), 8.55 (0.05H, d, *J* = 3.5 Hz), 8.43 (1H, d, *J* = 6.0 Hz), 8.3 (1H, s), 7.52 (0.05H, d, *J* = 8.0 Hz), 7.40 - 7.19 (11H, m), 7.07 (1H, dd, *J* = 8.0, 4.5 Hz), 6.88 (1H, s), 4.86 (2H, s), 3.385 (3H, s).

¹³C NMR (CDCl₃, 125 MHz): δ 169.4, 149.1, 148.24, 138.6, 135.83, 135.2, 134.1, 128.97, 128.74, 128.5, 128.27, 127.3, 127.2, 123.13, 82.57, 75.4, 57.38.

Mass Spectrum: [C₂₄H₂₆NO₃]⁺ observed 334.0 m/z calculated 334.1 m/z

(*S*)-MPA-(4-pyridyl)phenylmethanol (**IV.4l**): Colorless oil, 45 mg, quantitative yield

¹H NMR (CDCl₃, 500 MHz): δ 8.51 (2H, dd, *J* = 4.0, 1.5 Hz), 8.34 (2H, dd, *J* = 4.0, 1.5 Hz), 7.39 - 7.12 (18H, m), 7.01 (2H, dd, *J* = 7.5, 1.0 Hz), 6.78 (4H, m), 4.88 (1H, s), 4.86 (1H, s), 3.39 (3H, s), 3.38 (3H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 169.4, 169.3, 149.96, 149.74, 148.26, 148.2, 138.1, 137.95, 135.9, 135.7, 129.01, 128.82, 128.74, 128.72, 128.62, 128.54, 128.39, 128.06, 127.84, 127.51, 127.41, 127.18, 126.86, 121.4, 120.8, 82.61, 82.43, 76.05, 75.90, 57.38, 57.29.

Mass Spectrum: $[\text{C}_{24}\text{H}_{26}\text{NO}_3]^+$ observed 334.0 m/z calculated 334.1 m/z

(*R,S*)-MPA-(4-pyridyl)phenylmethanol (**(*R,S*)-IV.4I**): Colorless oil, 9 mg, 41%

Diastereomeric Ratio (**(*R,S*)-IV.4I**: **(*S,S*)-IV.4I**): 4:1

^1H NMR (CDCl_3 , 500 MHz): δ 8.51 (2H, dd, J = 5.5, 1.5 Hz), 8.34 (0.5H, dd, J = 4.0, 1.5 Hz), 7.45 - 7.12 (13H, m), 7.02 (2H, dd, J = 7.5, 1.5 Hz), 6.78 (2H, m), 4.88 (1H, s), 4.86 (0.25H, s), 3.395 (3H, s), 3.388 (0.75H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 169.4, 149.98, 149.76, 148.3, 137.97, 135.7, 129.01, 128.86, 128.78, 128.66, 128.57, 128.43, 128.17, 127.54, 127.45, 127.21, 126.89, 121.46, 120.89, 82.65, 76.07, 57.44.

Mass Spectrum: $[\text{C}_{24}\text{H}_{26}\text{NO}_3]^+$ observed 334.0 m/z calculated 334.1 m/z

(*S,S*)-MPA-(4-pyridyl)phenylmethanol (**(*S,S*)-IV.4I**): Colorless oil, 11 mg, 50%

Diastereomeric Ratio (**(*R,S*)-IV.4I**: **(*S,S*)-IV.4I**): 0:1

^1H NMR (CDCl_3 , 500 MHz): δ 8.36 (2H, dd, J = 6.5 Hz), 7.44 - 7.23 (10H, m), 6.79 (2H, d, J = 6.5 Hz), 4.86 (1H, s), 3.38 (3H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 169.3, 149.77, 148.35, 135.9, 129.06, 128.80, 128.78, 127.56, 127.45, 120.9, 82.47, 75.94, 57.33.

Mass Spectrum: $[\text{C}_{24}\text{H}_{26}\text{NO}_3]^+$ observed 334.0 m/z calculated 334.1 m/z

IV.6.9: General Procedure for Saponification (**IV.3a-I**)

The (*S*)-MPA ester isolated from prep-TLC was dissolved in THF (1 mL) in a 20 mL vial. NaOH (1% aq, 1 mL) was then added and the suspension was stirred for 12 hours. When the reaction was complete, as indicated by TLC, the reaction was diluted with water (10 mL) and CH₂Cl₂ (10 mL). The water was extracted with CH₂Cl₂ (5 mL, 3 xs). The organic layers were combined and dried with Na₂SO₄ then the solvent was removed under reduced pressure to provide the desired alcohol. The enantiomeric excess of the alcohol was determined by chiral HPLC.

(*R*)-1-(2-pyridyl)-hexan-1-ol (**(*R*)-IV.3a**): colorless oil, 6 mg, 86%, 80% *ee*

¹H NMR (CDCl₃, 500 MHz): δ 8.51 (1H, d, *J* = 4.0 Hz), 7.65 (1H, t, *J* = 7.5 Hz), 7.24 - 7.15 (2H, m), 4.71 (1H, dd, *J* = 7.0, 4.0 Hz), 4.13 (1H, br s), 1.79 (1H, m), 1.66 (1H, sextet, *J* = 7.0 Hz), 1.42-1.23 (6H, m), 0.85 (3H, t, *J* = 5.5 Hz).

¹³C NMR (CDCl₃, 125 MHz): δ 162.4, 148.2, 136.6, 122.2, 120.3, 72.8, 38.6, 31.8, 24.9, 22.6, 13.99.

Mass Spectrum: [C₁₁H₁₈NO]⁺ observed 180.1 m/z calculated 180.1 m/z

(*S*)-1-(2-pyridyl)-hexan-1-ol (**(*S*)-IV.3a**): colorless oil, 10.8 mg, 99%, >99% *ee*

¹H NMR (CDCl₃, 500 MHz): δ 8.52 (1H, d, *J* = 4.5 Hz), 7.65 (1H, t, *J* = 7.5 Hz), 7.24 - 7.15 (2H, m), 4.71 (1H, dd, *J* = 7.5, 5.0 Hz), 4.09 (1H, br s), 1.79 (1H, m), 1.66 (1H, sextet, *J* = 7.0 Hz), 1.42-1.23 (6H, m), 0.85 (3H, t, *J* = 6.0 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 162.3, 148.2, 136.6, 122.2, 120.3, 72.8, 38.6, 31.8, 24.9, 22.6, 14.0.

Mass Spectrum: $[\text{C}_{11}\text{H}_{18}\text{NO}]^+$ observed 180.1 m/z calculated 180.1 m/z

(*R*)-1-(2-pyridyl)-ethan-1-ol ((*R*)-**IV.3b**): yellow oil, 1.6 mg, 33%, 67% *ee*

Partial Data: ^1H NMR (CDCl_3 , 500 MHz): δ 8.52 (1H, s), 7.67 (1H, t, J = 6.5 Hz), 7.26 - 7.17 (2H, m), 4.87 (1H, q, J = 6.5 Hz), 4.22 (1H, br s), 1.48 (3H, d, J = 6.5 Hz).

Proton matched racemic alcohol (**IV.1b**).

Mass Spectrum: $[\text{C}_7\text{H}_{10}\text{NO}]^+$ observed 124.2 m/z calculated 124.1 m/z

(*S*)-1-(2-pyridyl)-ethan-1-ol ((*S*)-**IV.3b**): yellow oil, 1.3 mg, 35%, 67% *ee*

Partial Data: ^1H NMR (CDCl_3 , 500 MHz): δ 8.52 (1H, s), 7.67 (1H, t, J = 7.0 Hz), 7.26 - 7.17 (2H, m), 4.87 (1H, m), 1.49 (3H, d, J = 6.5 Hz).

Proton matched racemic alcohol (**IV.1b**).

Mass Spectrum: $[\text{C}_7\text{H}_{10}\text{NO}]^+$ observed 124.1 m/z calculated 124.1 m/z

(*S*)-1-(2-pyridyl)-2-methylpropan-1-ol ((*S*)-**IV.3c**): colorless oil, 3.6 mg, >99%, >99% *ee*

^1H NMR (CDCl_3 , 500 MHz): δ 8.60 (1H, d, J = 5.0 Hz), 7.87 (1H, dt, J = 7.5, 1.5 Hz), 7.44-7.36 (2H, m), 4.67 (1H, d, J = 5.5 Hz), 2.01 (1H, dsextet, J = 7.0, 1.5 Hz), 0.97 (3H, d, J = 6.5 Hz), 0.85 (3H, d, J = 6.5 Hz).

^{13}C NMR (CDCl_3 , 150 MHz): δ 161.5, 147.9, 136.4, 122.2, 121.0, 77.1, 35.1, 19.5, 16.0.

Mass Spectrum: $[\text{C}_9\text{H}_{14}\text{NO}]^+$ observed 152.1 m/z calculated 152.1 m/z

(*R*)-1-(2-pyridyl)-3-methylbutan-1-ol (**(*R*)-IV.3d**): yellow oil, 2.7 mg, 71%, >99% *ee*

¹H NMR (CDCl₃, 300 MHz): δ 8.61 (1H, d, *J* = 7.5 Hz), 7.90 (1H, t, *J* = 8.5 Hz), 7.47 - 7.38 (2H, m), 4.95 (1H, m), 1.93 (1H, m), 1.75 (1H, m), 1.55 (1H, m), 1.00 (3H, d, *J* = 5.5 Hz), 0.95 (3H, d, *J* = 6.0 Hz).

¹³C NMR (CDCl₃, 150 MHz): δ 162.97, 148.2, 136.6, 122.1, 120.2, 71.3, 47.9, 24.6, 23.5, 21.8.

Mass Spectrum: [C₁₀H₁₆NO]⁺ observed 166.1 m/z calculated 166.1 m/z

(*R*)-1-(2-pyridyl)-3-methylbutan-1-ol (**(*S*)-IV.3d**): colorless oil, 2.6 mg, 60%, >99% *ee*

¹H NMR (CDCl₃, 300 MHz): δ 8.61 (1H, d, *J* = 5.5 Hz), 7.90 (1H, dt, *J* = 7.0, 1.5 Hz), 7.47 - 7.38 (2H, m), 4.95 (1H, dd, *J* = 10.0, 4.0 Hz), 1.93 (1H, m), 1.75 (1H, m), 1.55 (1H, m), 1.00 (3H, d, *J* = 6.5 Hz), 0.95 (3H, d, *J* = 7.0 Hz).

¹³C NMR (CDCl₃, 150 MHz): δ 162.94, 148.1, 136.6, 122.1, 120.3, 71.3, 47.9, 24.7, 23.5, 21.8.

Mass Spectrum: [C₁₀H₁₆NO]⁺ observed 166.1 m/z calculated 166.1 m/z

(*R*)-1-(2-pyridyl)-heptadecan-1-ol (**(*R*)-IV.3e**): white solid, 10.5 mg, 51%, 67% *ee*

¹H NMR (CDCl₃, 300 MHz): δ 8.52 (1H, d, *J* = 5.0 Hz), 7.65 (1H, t, *J* = 7.5 Hz), 7.24 - 7.15 (2H, m), 4.71 (1H, dd, *J* = 7.5, 4.5 Hz), 4.09 (1H, br s), 1.78 (1H, m), 1.66 (1H, m), 1.41 - 1.2 (28H, m), 0.86 (3H, t, *J* = 6.5 Hz).

¹³C NMR (CDCl₃, 125 MHz): δ 162.3, 148.2, 136.5, 122.2, 120.3, 72.8, 38.7, 31.9, 29.68, 29.64, 29.61, 29.59, 29.56, 29.34, 25.3, 22.7, 14.1.

Mass Spectrum: [C₂₂H₄₀NO]⁺ observed 334.2 m/z calculated 334.3 m/z

Melting Point: 41 - 42 °C

(S)-1-(2-pyridyl)-hexan-1-ol ((**S**)-**IV.3e**): white solid, 16 mg, 64%, >99% *ee*

^1H NMR (CDCl_3 , 300 MHz): δ 8.52 (1H, d, J = 4.5 Hz), 7.65 (1H, t, J = 8.0 Hz), 7.24 - 7.15 (2H, m), 4.71 (1H, dd, J = 7.0, 4.5 Hz), 4.11 (1H, br s), 1.80 (1H, m), 1.66 (1H, m), 1.41 - 1.2 (28H, m), 0.86 (3H, t, J = 7.0 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 162.4, 148.2, 136.5, 122.2, 120.3, 72.8, 38.7, 31.9, 29.68, 29.64, 29.61, 29.59, 29.56, 29.34, 25.3, 22.7, 14.1.

Mass Spectrum: $[\text{C}_{22}\text{H}_{40}\text{NO}]^+$ observed 334.2 m/z calculated 334.3 m/z

Melting Point: 39 - 40 $^{\circ}\text{C}$

(R)-1-(3-pyridyl)-hexan-1-ol ((**R**)-**IV.3f**): colorless oil, 3.2 mg, >99%, 95% *ee*

^1H NMR (CDCl_3 , 500 MHz): 8.55 (1H, s), 8.49 (1H, s), 7.68 (1H, d, J = 7.5 Hz), 7.28 - 7.24 (1H, m), 4.71 (1H, t, J = 7.0 Hz), 1.80 (1H, m), 1.71 (1H, m), 1.42 - 1.23 (6H, m), 0.85 (3H, t, J = 7.0 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 148.9, 147.9, 133.5, 115.8, 109.98, 39.1, 31.6, 25.3, 22.5, 13.9.

Mass Spectrum: $[\text{C}_{11}\text{H}_{18}\text{NO}]^+$ observed 180.1 m/z calculated 180.1 m/z

(S)-1-(3-pyridyl)-hexan-1-ol ((**S**)-**IV.3f**): colorless oil, 3.9 mg, 89%, >99% *ee*

^1H NMR (CDCl_3 , 500 MHz): δ 8.55 (1H, s), 8.49 (1H, s), 7.68 (1H, d, J = 7.0 Hz), 7.28 - 7.24 (1H, m), 4.71 (1H, t, J = 6.0 Hz), 1.80 (1H, m), 1.71 (1H, m), 1.42 - 1.23 (6H, m), 0.85 (3H, t, J = 7.0 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 149.0, 147.9, 133.7, 115.8, 109.94, 39.1, 31.6, 25.3, 22.5, 13.9.

Mass Spectrum: $[\text{C}_{11}\text{H}_{18}\text{NO}]^+$ observed 180.1 m/z calculated 180.1 m/z

(*S*)-1-(2-pyridyl)-hexan-1-ol (**(*S*)-IV.3g**): colorless oil, 6.3 mg, >99%, >99% *ee*

^1H NMR (CDCl_3 , 500 MHz): δ 8.51 (2H, d, J = 5.0 Hz), 7.24 (2H, d, J = 6.0 Hz), 4.67 (1H, t, J = 5.5 Hz), 1.70 (2H, m), 1.40 - 1.22 (6H, m), 0.85 (3H, t, J = 5.5 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 149.7, 120.8, 73.0, 38.9, 31.6, 25.1, 22.5, 13.9.

Mass Spectrum: $[\text{C}_{11}\text{H}_{18}\text{NO}]^+$ observed 180.1 m/z calculated 180.1 m/z

(*R*)-(2-pyridyl)phenylmethanol (**(*R*)-IV.3h**): White solid, 6.7 mg, 96%, 91% *ee*

^1H NMR (CDCl_3 , 300 MHz): δ 8.54 (1H, s), 7.59 (1H, t, J = 2.5 Hz), 7.36-7.12 (7H, m), 5.73 (1H, s), 5.25 (1H, br s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 160.9, 147.8, 143.2, 136.8, 128.6, 127.8, 127.1, 122.4, 121.3, 74.9.

Mass Spectrum: $[\text{C}_{12}\text{H}_{12}\text{NO}]^+$ observed 186.1 m/z calculated 186.1 m/z

Melting Point: 48 - 51 $^{\circ}\text{C}$

(*S*)-(2-pyridyl)phenylmethanol (**(*S*)-IV.3h**): White solid, 8.6 mg, 99%, >99% *ee*

^1H NMR (CDCl_3 , 300 MHz): δ 8.53 (1H, d, J = 3.0 Hz), 7.59 (1H, t, J = 2.5 Hz), 7.36-7.12 (7H, m), 5.73 (1H, s), 5.25 (1H, br s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 160.8, 147.8, 143.2, 136.8, 128.6, 127.8, 127.1, 122.5, 121.5, 74.9.

Mass Spectrum: $[\text{C}_{12}\text{H}_{12}\text{NO}]^+$ observed 186.1 m/z calculated 186.1 m/z

Melting Point: 47 - 50 $^{\circ}\text{C}$

(*R*)-(2-pyridyl)mesitylmethanol ((***R***)-**IV.3i**): White solid, 9.1 mg, 76%, 75% *ee*

¹H NMR (CDCl₃, 500 MHz): δ 8.56 (1H, d, *J* = 4.5 Hz), 7.55 (1H, t, *J* = 7.0 Hz), 7.17 (1H, t, *J* = 5.0 Hz), 6.88 (1H, d, *J* = 7.0 Hz), 6.81 (2H, s), 6.17 (1H, s), 5.35 (1H, br s), 2.24 (3H, s), 2.17 (6H, s).

¹³C NMR (CDCl₃, 125 MHz): δ 161.3, 147.4, 137.5, 137.3, 136.8, 134.9, 129.9, 121.8, 120.4, 70.4, 20.9, 20.3.

Mass Spectrum: [C₁₅H₁₈NO]⁺ observed 228.0 m/z calculated 228.1 m/z

Melting Point: 59 - 63 °C

(*S*)-(2-pyridyl)mesitylmethanol ((***S***)-**IV.3i**): White solid, 13.2 mg, >99%, >99% *ee*

¹H NMR (CDCl₃, 500 MHz): δ 8.57 (1H, s), 7.55 (1H, t, *J* = 7.5 Hz), 7.18 (1H, t, *J* = 5.0 Hz), 6.88 (1H, d, *J* = 7.5 Hz), 6.81 (2H, s), 6.17 (1H, s), 5.35 (1H, br s), 2.25 (3H, s), 2.17 (6H, s).

¹³C NMR (CDCl₃, 125 MHz): δ 161.3, 147.4, 137.5, 137.4, 136.4, 134.99, 129.97, 121.8, 120.4, 70.4, 20.9, 20.3.

Mass Spectrum: [C₁₅H₁₈NO]⁺ observed 228.1 m/z calculated 228.1 m/z

Melting Point: 58 - 61 °C

(*R*)-(2-pyridyl)tolylmethanol ((***R***)-**IV.3j**): Brown semi-solid, 12 mg, >99%, 91% *ee*

¹H NMR (CDCl₃, 500 MHz): δ 8.54 (1H, s), 7.60 (1H, t, *J* = 3.0 Hz), 7.25 - 7.11 (6H, m), 5.70 (1H, s), 5.18 (1H, br s), 2.31 (3H, s).

¹³C NMR (CDCl₃, 150 MHz): δ 161.1, 147.7, 140.3, 137.5, 136.8, 129.2, 127.0, 122.3, 121.3, 74.8, 21.1.

Mass Spectrum: [C₁₃H₁₄NO]⁺ observed 200.1 m/z calculated 200.1 m/z

(*S*)-(2-pyridyl)tolylmethanol (**(S)-IV.3j**): Brown semi-solid, 12.2 mg, >99%, >99% *ee*

^1H NMR (CDCl_3 , 500 MHz): δ 8.54 (1H, s), 7.60 (1H, t, $J = 4.5$ Hz), 7.25 - 7.11 (6H, m), 5.70 (1H, s), 5.17 (1H, br s), 2.31 (3H, s).

^{13}C NMR (CDCl_3 , 150 MHz): δ 161.1, 147.8, 140.3, 137.5, 136.8, 129.2, 127.0, 122.3, 121.3, 74.8, 21.1.

Mass Spectrum: $[\text{C}_{13}\text{H}_{14}\text{NO}]^+$ observed 200.1 m/z calculated 200.1 m/z

(*R*)-(3-pyridyl)phenylmethanol (**(R)-IV.3k**): White solid, 5.6 mg, 37%, 91% *ee*

^1H NMR (CDCl_3 , 500 MHz): δ 8.58 (1H, s), 8.45 (1H, s), 7.67 (1H, d, $J = 7.5$ Hz), 7.39 - 7.21 (6H, m), 5.86 (1H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 148.7, 148.2, 143.0, 134.1, 128.8, 128.0, 126.5, 123.4, 74.2.

Mass Spectrum: $[\text{C}_{12}\text{H}_{12}\text{NO}]^+$ observed 186.1 m/z calculated 186.1 m/z

(*S*)-(3-pyridyl)phenylmethanol (**(S)-IV.3k**): White solid, 4.4 mg, 29%, 95% *ee*

^1H NMR (CDCl_3 , 500 MHz): δ 8.59 (1H, s), 8.46 (1H, s), 7.66 (1H, d, $J = 7.8$ Hz), 7.38 - 7.11 (6H, m), 5.86 (1H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 148.8, 148.3, 143.2, 134.1, 128.7, 128.1, 126.5, 123.4, 74.2.

Mass Spectrum: $[\text{C}_{12}\text{H}_{12}\text{NO}]^+$ observed 186.1 m/z calculated 186.1 m/z

(*R*)-(4-pyridyl)phenylmethanol (**(R)-IV.3l**): Off-white solid, 7.6 mg, >99%, 80% *ee*

^1H NMR (CDCl_3 , 500 MHz): δ 8.44 (1H, d, $J = 4.5$ Hz), 7.34 - 7.22 (7H, m), 5.76 (1H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 149.5, 128.79, 128.21, 128.19, 127.8, 126.8, 121.3, 74.9.

Mass Spectrum: $[\text{C}_{12}\text{H}_{12}\text{NO}]^+$ observed 186.1 m/z calculated 186.1 m/z

Melting Point: 132 - 135 °C

(*S*)-(2-pyridyl)phenylmethanol (**(S)-IV.3I**): Off-white solid, 8.9 mg, >99%, >99% *ee*

^1H NMR (CDCl_3 , 500 MHz): δ 8.48 (1H, d, J = 6.0 Hz), 7.34 - 7.29 (7H, m), 5.77 (1H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 149.7, 128.76, 128.3, 126.8, 121.2, 75.0.

Mass Spectrum: $[\text{C}_{12}\text{H}_{12}\text{NO}]^+$ observed 186.1 m/z calculated 186.1 m/z

Melting Point: 129 - 131 °C

($\pm$)-*O,O*-dimethylannocherin A (**IV.5**): In a dry 50 mL, 2-neck flask under Ar, magnesium turnings (24 mg, 0.97 mmol, 7 equiv) was added to diethyl ether (dry, 1 mL). *p*-bromoanisole (86 μL , 129 mg, 0.69 mmol, 5 equiv) dissolved in diethyl ether (dry, 1 mL) was added to the magnesium turnings. Bubbling was observed which was taken as an indication that the Grignard was forming. After 30 minutes, 6,7-dimethoxyisoquinoline-1-carboxaldehyde (30 mg, 0.14 mmol, 1 equiv) dissolved in diethyl ether (dry, 1 mL) was slowly added to the Grignard. After 4 hours, the reaction was quenched with NH_4Cl (sat. aq.). The reaction was diluted with NH_4Cl (sat. aq., 5 mL) and CH_2Cl_2 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL, 3 xs). The organics were combined and dried with brine (sat. aq., 10 mL) and Na_2SO_4 followed by removal of the solvent under reduced pressure. The crude product was purified by column chromatography (50 % EtOAc/hexanes) as a brown solid (31 mg, 70%).

(IV.5): ^1H NMR (CDCl_3 , 500 MHz): δ 8.38 (1H, d, J = 6.0 Hz), 7.48 (1H, d, J = 6.0 Hz), 7.21 (2H, d, J = 7.0 Hz), 7.05 (2H, d, J = 6.0 Hz), 6.80 (2H, d, J = 6.5 Hz), 6.13 (1H, s), 3.96 (3H, s), 3.77 (3H, s), 3.73 (3H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 159.2, 156.7, 152.7, 149.8, 138.8, 135.8, 132.96, 128.9, 120.9, 119.75, 114.1, 105.2, 103.3, 72.3, 56.0, 55.8, 55.2.

Mass Spectrum: $[\text{C}_{19}\text{H}_{20}\text{NO}_4]^+$ observed 326.0 m/z calculated 326.1 m/z

Enantiomers separated by chiral HPLC. AD-H, 98:2 Hexanes:Isopropyl alcohol, 25 and 29 min

1,2-dimethoxy-4-(2-nitrovinyl)benzene **(IV.6)**: In a 250 mL flask, PCC (10g, 46 mmol, 1.1 equiv) was dissolved in CH_2Cl_2 (dry, 85 mL) while stirring under N_2 . Veratryl alcohol (3,4-dimethoxybenzyl alcohol, 4.6 mL, 7.1 g, 42 mmol, 1 equiv) was dissolved in CH_2Cl_2 (dry, 40 mL) and was then added slowly to the flask containing the PCC. The reaction was stirred over night then the reaction mixture was filtered through a silica plug. The silica plug was flushed with EtOAc. The filtrate was collected and the solvent was removed under reduced pressure. The dark crude product was purified by column chromatography (50% EtOAc/Hexanes) to provide the desired product as an off-white solid (5.76 g, 82%).

Aldehyde: ^1H NMR (CDCl_3 , 300 MHz): δ 9.83 (1H, s), 7.46 - 7.39 (2H, m), 6.96 (1H, d, J = 8.1 Hz), 3.95 (3H, s), 3.93 (3H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 190.8, 154.46, 149.6, 130.1, 126.8, 110.36, 108.9, 56.1, 55.95.

Mass Spectrum: $[\text{C}_9\text{H}_{10}\text{O}_3]^+$ observed 167.1 m/z calculated 167.1 m/z

Melting Point: 33 - 36 $^\circ\text{C}$

The veratryl aldehyde (5.15 g, 30 mmol, 1 equiv), nitromethane (6.63 mL, 9.15 g, 150 mmol, 5 equiv), ammonium acetate (2.31 g, 30 mmol, 1 equiv) and acetic acid (5.1 mL) were added to a 50 mL flask. The reaction was refluxed for 1.5 hours then the flask was cooled to room temperature then chilled in an ice bath over 2 hours. The desired product crashes out of solution as a yellow solid upon cooling. The product is filtered and washed with cool EtOH to provide the desired product as a yellow solid (6 g, 96%).

(IV.6): ^1H NMR (CDCl_3 , 500 MHz): δ 7.94 (1H, d, $J = 14.0$ Hz), 7.51 (1H, d, $J = 13.5$), 7.16 (1H, dd, $J = 8.5, 2.0$ Hz), 6.99 (1H, d, $J = 1.5$ Hz), 6.90 (1H, d, $J = 8.5$ Hz), 3.93 (3H, s), 3.91 (3H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 152.8, 149.55, 139.26, 135.15, 124.6, 122.8, 111.3, 110.3, 56.1, 55.98.

IR: 1489, 1278, 1230, 978, 806 cm^{-1}

Mass Spectrum: $[\text{C}_{10}\text{H}_{12}\text{NO}_4]^+$ observed 210.0 m/z calculated 210.1 m/z

Melting Point: 124 - 126 $^{\circ}\text{C}$

1,2-dimethoxy-4-(*N*-acetyl-2-aminoethyl)benzene (**IV.7**): In a flame dried round bottom flask, LAH (2 g, 52 mmol, 2 equiv) was suspended in THF (dry, 40 mL). 1,2-dimethoxy-4-(2-nitrovinyl)benzene (5.5 g, 26 mmol, 1 equiv) was suspended in THF (60 mL). The suspension of the substrate was added slowly to the LAH suspension, and the reaction mixture was heated to reflux. The reaction was complete in 3 hours and the reaction was cooled to room temperature. The LAH was quenched with KOH (2 M) until bubbling ceased. The reaction mixture was filtered over celite. The celite was washed with MeOH and the filtrate was

collected. Removal of the solvent provided the amine as a yellow solid (4.6 g, 98%) with minor impurities which was taken to the acylation without further purification.

Amine: ^1H NMR (CDCl_3 , 300 MHz): δ 6.80 - 6.70 (3H, m), 3.85 (3H, s), 3.83 (3H, s), 2.92 (2H, t, J = 6.9 Hz), 2.67 (2H, t, J = 6.9 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 148.9, 147.4, 131.99, 120.6, 111.99, 111.3, 55.82, 55.72, 43.2, 38.96.

Mass Spectrum: $[\text{C}_{10}\text{H}_{16}\text{NO}_2]^+$ observed 182.1 m/z calculated 182.12 m/z

Melting Point: 71 - 73 °C

In a flame dried 50 mL flask under N_2 , 1,2-dimethoxy-4-(2-aminoethyl)benzene (560 mg, 3.1 mmol, 1 equiv) was dissolved in CH_2Cl_2 (dry, 12 mL) to which triethylamine (432 μL , 313.6 mg, 3.1 mmol, 1 equiv) and acetyl chloride (270 μL , 375 mg, 4.77 mmol, 1.5 equiv) were added. The reaction was stirred overnight then was quenched with NH_4Cl (sat. aq.) and diluted with CH_2Cl_2 (10 mL) and water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL, 3 xs) and the organics were combined, dried with brine (sat. aq., 20 mL) and Na_2SO_4 then the solvent was removed under reduced pressure to provide the desired product as a yellow solid (605 mg, 87%)

(IV.7): ^1H NMR (CDCl_3 , 300 MHz): δ 6.80 - 6.76 (3H, m), 5.56 (1H, br s), 3.83 (3H, s), 3.82 (3H, s), 3.45 (2H, q, J = 6.9 Hz), 2.72 (2H, t, J = 7.2 Hz), 1.90 (3H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 169.95, 149.0, 147.7, 131.3, 120.6, 111.89, 111.38, 55.88, 55.84, 40.7, 35.15, 23.3.

Mass Spectrum: $[\text{C}_{12}\text{H}_{18}\text{NO}_3]^+$ observed 224.1 m/z calculated 224.1 m/z

Melting Point: 76 - 79 °C

2,3-dihydro-6,7-dimethoxy-1-methylisoquinoline (**IV.8**): The 1,2-dimethoxy-4-(*N*-acetyl-2-aminoethyl)benzene (1 g, 4.5 mmol, 1 equiv) was dissolved in toluene (dry, 20 mL) in a dry 50 mL flask under N₂. Phosphorous oxychloride (0.75 mL, 1.23 g, 8.05 mmol, 1.8 equiv) was added and the reaction was refluxed and monitored by TLC. After 1 hour the reaction was cooled to room temperature then chilled in an ice bath. To quench the reaction, NaHCO₃ (sat. aq., 5 mL) was added and the reaction was diluted with NaHCO₃ (sat. aq., 10 mL) and CH₂Cl₂ (10 mL). The aqueous layer was extracted with CH₂Cl₂ (20 mL, 3 xs). The organics were combined and washed with NaHCO₃ (sat. aq., 50 mL) and dried with Na₂SO₄. The solvent was removed under reduced pressure to provide the crude product which was purified by gradient column chromatography (100 % CH₂Cl₂ - 100 % EtOAc - 20% MeOH/CH₂Cl₂/1 % Et₃N) to give the desired product as a tan solid (890 mg, 96%).

(**IV.8**): ¹H NMR (CDCl₃, 300 MHz): δ 6.97 (1H, s), 6.66 (1H, s), 3.89 (3H, s), 3.88 (3H, s), 3.61 (2H, qt, *J* = 7.5, 1.5 Hz), 2.61 (2H, dd, *J* = 7.8, 1.8), 2.34 (3H, t, 1.5 Hz), 1.79 (1H, br s).

¹³C NMR (CDCl₃, 150 MHz): δ 163.86, 150.9, 147.3, 130.97, 122.05, 110.1, 108.99, 46.4, 25.5, 22.9.

Mass Spectrum: [C₁₂H₁₆NO₂]⁺ observed 210.0 m/z calculated 210.08 m/z

Melting Point: 74 - 79 °C

6,7-dimethoxyisoquinoline-1-carboxaldehyde (**IV.9**): 2,3-dihydro-6,7-dimethoxy-1-methylisoquinoline (10 mg, 2.0 mmol, 1 equiv) was dissolved in chlorobenzene (3 mL) in a 50 mL two neck flask. Manganese dioxide (85.2 mg, 0.98 mmol, 20 equiv) was added and the reaction was refluxed. After 18 hours, the reaction was filtered over celite. The celite was

washed with methanol and the filtrate was collected. The solvent was removed under reduced pressure to provide the crude product (a mixture of isoquinoline and isoquinoline aldehyde in a 2:1 ratio). The mixture was purified by gradient column chromatography (100 % EtOAc - 100 % Acetone) to provide the aldehyde as an orange solid (6 mg, 57%). The isoquinoline was isolated at (20 % MeOH/CH₂Cl₂).

Isoquinoline: ¹H NMR (CDCl₃, 500 MHz): δ 8.25 (1H, d, *J* = 6.0 Hz), 7.40 (1H, d, *J* = 6.0 Hz), 7.27 (1H, s), 7.06 (1H, s), 4.03 (3H, s), 4.02 (3H, s), 2.91 (3H, s).

Mass Spectrum: [C₁₂H₁₆NO₂]⁺ observed 206.1 m/z calculated 206.1 m/z

(IV.9): ¹H NMR (CDCl₃, 300 MHz): δ 10.41 (1H, s), 8.73 (1H, s), 8.60 (1H, d, *J* = 5.4 Hz), 7.75 (1H, d, *J* = 5.4 Hz), 7.13 (1H, s), 4.08 (3H, s), 4.04 (3H, s).

¹³C NMR (CDCl₃, 125 MHz): δ 196.4, 153.16, 152.9, 147.3, 141.6, 134.4, 123.97, 123.2, 104.56, 103.46, 56.26, 56.0.

Mass Spectrum: [C₁₂H₁₄NO₃]⁺ observed 218.0 m/z calculated 218.1 m/z

1-(2-pyridyl)-heptan-2-ol (**IV.11**): To an oven dried 50 mL flask, picoline (124 μL, 186 mg, 2 mmol, 1 equiv) was dissolved in diethyl ether (dry, 10 mL) while stirring under N₂. The flask was chilled to 0 °C in an ice bath and *n*BuLi (2.5 mL, 4 mmol, 2 equiv) was added over 10 minutes. The flask was slowly warmed to room temperature and was stirred for 30 minutes generating the dark red picoline anion.

In a 20 mL vial, magnesium bromide (1.01 g, 5.5 mmol, 2.75 equiv) were dried under vacuum while heated with a heat gun for 30 minutes. The vial was cooled and back filled with N₂. To the vial, diethyl ether (dry, 2 mL) were added and the suspension was added to the flask

with the picoline anion which was chilled to 0 °C in an ice bath. The flask was slowly warmed to room temperature then was stirred for 30 minutes.

Hexanal (737 μ L, 601 mg, 6 mmol, 3 equiv) was dissolved in diethyl ether (dry, 10 mL) in a 20 mL vial. The flask containing the picoline anion was chilled to 0 °C in an ice bath then the hexanal was added dropwise. The reaction was monitored by TLC, showing completion after 3 hours. The reaction was quenched by slow addition of NH₄Cl (sat. aq., 10 mL) and was warmed to room temperature. The reaction was diluted with CH₂Cl₂ (10 mL and water 10 mL). The water layer was extracted with CH₂Cl₂ (30 mL, 3 xs). The CH₂Cl₂ was combined and dried with Na₂SO₄ and the solvent was removed under reduced pressure. The crude product was dissolved in CH₂Cl₂ (30 mL), and extracted with HCl (10 % aq, 30 mL, 3 xs). The HCl layers were combined and basified by slow addition of NaHCO₃ (solid powder) until bubbling ceased. The aqueous solution was extracted with CH₂Cl₂ (40 mL, 3 xs). The CH₂Cl₂ was combined, dried with Na₂SO₄ and the solvent was removed under reduced pressure to provide the desired product as a yellow oil (314 mg, 81%).

(**IV.11**): ¹H NMR (CDCl₃, 300 MHz): δ 8.74 (1H, ddd, J = 4.8, 2.1, 1.2 Hz), 7.59 (1H, dt, J = 7.8, 1.8 Hz), 7.13 (2H, m), 4.02 (1H, m), 2.94 - 2.77 (2H, m), 1.59 - 1.29 (8H, m), 0.87 (3H, t, J = 6.9 Hz).

¹³C NMR (CDCl₃, 150 MHz): δ 160.3, 148.5, 136.7, 123.7, 121.4, 71.0, 43.3, 37.1, 31.9, 25.3, 22.6, 14.0.

Mass Spectrum: [C₁₂H₂₀NO]⁺ observed 194.1 m/z calculated 194.15 m/z

(S)-MPA-1-(2-pyridyl)-heptan-2-ol (**IV.12**):

Same procedure as described for **IV.4a-IV.4l**. Yellow oil, 42 mg, 95%

^1H NMR (CDCl_3 , 500 MHz): δ 8.46 (1H, dd, J = 6.0, 2.0 Hz), 8.35 (1H, dd, J = 5.0, 1.0 Hz), 7.47 (1H, dt, J = 8.0, 2.0 Hz), 7.34 - 7.22 (11H, m), 7.05 (2H, m), 6.94 (1H, dd, J = 7.5, 5.0 Hz), 6.62 (1H, d, J = 8.0 Hz), 5.30 (2H, m), 4.63 (1H, s), 4.61 (1H, s), 3.29 (3H, s), 3.26 (3H, s), 2.98 - 2.83 (4H, m), 1.59 (2H, m), 1.47 (2H, m), 1.31 - 1.18 (6H, m), 1.08 - 0.95 (6H, m), 0.82 (3H, t, J = 6.5 Hz), 0.73 (3H, t, J = 7.0 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 179.1, 170.0, 157.78, 157.40, 149.26, 149.09, 136.41, 136.33, 136.11, 135.93, 128.47, 128.42, 128.39, 127.17, 127.05, 123.57, 123.36, 121.42, 121.24, 82.59, 82.57, 74.89, 74.77, 57.22, 57.16, 42.99, 42.65, 34.0, 33.90, 31.45, 31.30, 24.82, 24.41, 22.40, 22.29, 13.87, 13.78.

Mass Spectrum: $[\text{C}_{21}\text{H}_{28}\text{NO}_3]^+$ observed 342.1 m/z calculated 342.2 m/z

(*S*)-MPA-1*R*-(2-pyridyl)-heptan-2-ol (**(*R,S*)-IV.12**): Colorless oil, 13.1 mg, 62%

Diastereomeric Ratio (**(*R,S*)-IV.12**):(**(*S,S*)-IV.12**): 10:1

^1H NMR (CDCl_3 , 500 MHz): δ 8.47 (1H, dd, J = 4.5 Hz), 8.37 (0.1H, s), 7.49 (1H, dt, J = 7.5 Hz), 7.36 - 7.22 (5H, m), 7.07 (2H, m), 5.29 (1H, pentet, J = 6.5 Hz), 4.63 (1H, s), 3.28 (3H, s), 3.00 (2H, m), 1.49 (2H, m), 1.08 - 0.95 (6H, m), 0.73 (3H, t, J = 7.0 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 170.15, 157.81, 149.29, 136.44, 136.18, 128.51, 128.44, 127.09, 123.62, 121.48, 82.61, 74.81, 57.27, 43.01, 33.94, 31.34, 24.45, 22.33, 13.83.

Mass Spectrum: $[\text{C}_{21}\text{H}_{28}\text{NO}_3]^+$ observed 342.1 m/z calculated 342.2 m/z

(*S*)-MPA-1*S*-(2-pyridyl)-heptan-2-ol (**(*S,S*)-IV.12**): Colorless oil, 12.9, 61%

Diastereomeric Ratio (**(*R,S*)-IV.12**):(**(*S,S*)-IV.12**): 1:20

^1H NMR (CDCl_3 , 500 MHz): δ 8.46 (0.05H, s), 8.37 (1H, d, J = 5.0 Hz), 7.34 - 7.22 (6H, m), 6.96 (1H, dd, J = 6.5, 4.5 Hz), 6.64 (1H, d, J = 7.5 Hz), 5.32 (1H, pentet, J = 6.0 Hz), 4.64 (1H, s), 3.31 (3H, s), 2.99 - 2.84 (2H, m), 1.59 (2H, m), 1.47 (2H, m), 1.31 - 1.18 (6H, m), 0.83 (3H, t, J = 7.0 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 170.0, 157.44, 149.11, 136.37, 135.99, 128.47, 127.21, 123.40, 121.28, 82.63, 74.94, 57.21, 42.68, 34.0, 31.5, 24.85, 22.45, 13.92.

Mass Spectrum: $[\text{C}_{21}\text{H}_{28}\text{NO}_3]^+$ observed 342.1 m/z calculated 342.2 m/z

1*R*-(2-pyridyl)-heptan-2-ol (**(R)-IV.11**): yellow oil, >99%, 91% *ee*

Same procedure as the hydrolysis of **IV.3a - IV.3l**

^1H NMR (CDCl_3 , 500 MHz): δ 8.47 (1H, d, J = 3.5 Hz), 7.59 (1H, dt, J = 7.5, 1.0 Hz), 7.12 (2H, m), 4.95 (1H, br s), 4.02 (1H, s), 2.92 - 2.78 (2H, m), 1.59 - 1.23 (8H, m), 0.87 (3H, t, J = 7.0 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 160.4, 148.6, 136.7, 123.7, 121.4, 71.0, 43.3, 37.1, 31.9, 25.3, 22.6, 14.0.

Mass Spectrum: $[\text{C}_{12}\text{H}_{20}\text{NO}]^+$ observed 194.1 m/z calculated 194.2 m/z

1*S*-(2-pyridyl)-heptan-2-ol (**(S)-IV.11**): yellow oil, 90%, 95% *ee*

Same procedure as the hydrolysis of **IV.3a - IV.3l**

^1H NMR (CDCl_3 , 500 MHz): δ 8.46 (1H, s), 7.59 (1H, t, J = 7.5 Hz), 7.12 (2H, m), 5.03 (1H, br s), 4.01 (1H, s), 2.92 - 2.78 (2H, m), 1.57 - 1.23 (8H, m), 0.87 (3H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 160.5, 148.6, 136.7, 123.7, 121.4, 71.0, 43.3, 37.1, 31.9, 25.3, 22.6, 14.0.

Mass Spectrum: $[\text{C}_{12}\text{H}_{20}\text{NO}]^+$ observed 194.1 m/z calculated 194.2 m/z

(3*R*)-1-(2-pyridyl)-butan-3-ol (**(*R*)-IV.13**): In a 100 mL flask under Ar, 2-picoline (62 μL , 93 mg, 1 mmol, 1 equiv) was dissolved in diethyl ether (5 mL). The flask was chilled to 0 °C in an ice bath. *n*-Butyllithium (1.25 mL, 2 mmol, 2 equiv) was added dropwise and the reaction was slowly warmed to room temperature. After 1 hour at room temperature, the flask was a deep red color indicating that the picoline anion had been generated. The reaction was again chilled to 0 °C in an ice bath then (*R*)-propylene oxide (175 μL , 145 mg, 2.5 mmol, 2.5 equiv) was slowly added. The reaction was monitored visually and by TLC. As the anion reacts, the vessel slowly turns yellow. After 4 hours the reaction was no longer red and complete conversion was indicated by TLC. The reaction was quenched by slow addition of water until bubbling ceased. The reaction was diluted with diethyl ether (10 mL) and water (10 mL), and the aqueous layer was extracted with diethyl ether (10 mL, 3 xs). The ether layers were combined and washed with brine (NaCl, aq. sat., 30 mL) then dried with MgSO_4 . The solvent was removed under reduced pressure to give the crude alcohol which was purified by gradient column chromatography (50% EtOAc/hexanes/1% Et_3N to 100% EtOAc/1% Et_3N). The desired product was isolated as a yellow oil (96 mg, 63%).

(*R*)-IV.13: ^1H NMR (CDCl_3 , 300 MHz): δ 8.46 (1H, ddd, J = 4.8, 1.8, 0.9 Hz), 7.59 (1H, dt, J = 7.5, 1.8 Hz), 7.17 - 7.08 (2H, m), 3.83 (1H, m), 2.95 (2H, m), 1.95 - 1.74 (2H, m), 1.20 (3H, d, J = 6.9 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 161.8, 148.2, 136.7, 122.9, 121.1, 66.6, 38.1, 34.3, 23.8.

Mass Spectrum: $[\text{C}_9\text{H}_{14}\text{NO}]^+$ observed 152.1 m/z calculated 152.1 m/z

2-acylpyrrole (**IV.14**): To a 100 mL round bottom flask, pyrrole (0.693 mL, 0.67 g, 10 mmol, 1 equiv), acetyl chloride (1.1 mL, 1.17 g, 15 mmol, 1.5 equiv), zinc dust (1.3 g, 20 mmol, 2 equiv) and toluene (20 mL, dry) were added. This suspension was stirred for 1 hour at room temperature and was quenched with NaHCO₃ (aq sat, 30 mL). The mixture was extracted with ethyl acetate (30 mL, 3 xs). The organics were combined and dried with Na₂SO₄ and the solvent was removed under reduced pressure to provide the crude as a dark oil. The crude was purified by column chromatography (10% EtOAc/hexanes) to provide a mixture of 2- and 3-acylpyrrole. This was again purified by column chromatography (5% EtOAc/hexanes) to provide the desired product **IV.14** as a dark oil (270 mg, 25%).^{80,81}

(**IV.14**): ¹H NMR (CDCl₃, 500 MHz): δ 9.71 (1H, br s), 7.03-7.01 (1H, m), 6.90-6.88 (1H, m), 6.26-6.24 (1H, m), 2.42 (3H, s).

Matches literature reported spectra.⁸⁰

R-1-(pyrrol-2-yl)ethanol: To a flame dried 25mL round bottom flask, (*S*)-2-methyloxazaborolidine (0.02 mL, 0.02 mmol, 0.01 equiv) and borane-dimethylsulfide complex (0.7 mL, 1.4 equiv, 0.7 equiv) were added at room temperature under N₂. This was stirred for 1 hour and 2-acetylpyrrole (218.3 mg, 2 mmol, 1 equiv) was added slowly. The reaction was stirred for another hour and was cooled to 0 °C and quenched with HCl/MeOH. This was extracted with ethyl acetate (10 mL, 3 xs). The organics were combined and dried with Na₂SO₄ and the solvent was removed under reduced pressure. Crude NMR showed no indication of starting material or the desired product.

N-Boc-2-acetylpyrrole (**IV.15**): Sodium hydride (44.2 mg, 1.1 mmol, 1.2 equiv) was suspended in THF (5.5 mL, dry) in a 50 mL round bottom flask under N₂ at room temperature. 2-acetylpyrrole (100 mg, 0.92 mmol, 1 equiv) was dissolved in THF (2 mL, dry) and added slowly to the NaH suspension. After 1 hour, Boc anhydride (218.3 mg, 1.0 mmol, 1.1 equiv) was added and the mixture was left to stir for 13 hours. NH₄Cl (aq sat, 5 mL) and H₂O (25 mL) were added to quench the reaction. The aqueous layer was extracted with ethyl acetate (30 mL, 3 xs). The organics were combined and washed with brine (50 mL) then dried with Na₂SO₄. The solvent was removed under reduced pressure to give the crude product as a brown oil. The NMR showed minor impurities therefore, it was not further purified prior to the next reaction (44 mg, 23%).⁸¹

(**IV.15**): ¹H NMR (CDCl₃, 500 MHz): δ 7.30 (1H, m), 6.83 (1H, m), 6.14 (1H, m), 2.43 (3H, s), 1.55 (9H, s).

Matches literature reported spectra.⁸¹

R,N-Boc-1-(pyrrol-2-yl)ethanol: To a flame dried 25 mL round bottom flask, (*S*)-2-methyloxazaborolidine (3.58 μL, 3.58 μmol, 0.01 equiv) and borane-dimethylsulfide complex (125 μL, 0.25 mmol, 0.7 equiv) were added at room temperature under N₂. This was stirred for 1 hour and *N*-Boc-2-acetylpyrrole (**IV.15**, 75 mg, 0.358 mmol, 1 equiv) was added slowly. The reaction was stirred for another hour and was cooled to 0 °C and quenched with HCl/MeOH. This was extracted with ethyl acetate (10 mL, 3 xs). The organics were combined and dried with Na₂SO₄, and the solvent was removed under reduced pressure. Crude NMR showed no indication of starting material or the desired product.

S,N-Boc-1-(pyrrol-2-yl)ethanol: To a flame dried 25 mL round bottom flask, (*R*)-2-methyloxazaborolidine (3.58 μ L, 3.58 μ mol, 0.01 equiv) and borane-dimethylsulfide complex (125 μ L, 0.25 mmol, 0.7 equiv) were added at room temperature under N₂. This was stirred for 1 hour and *N*-Boc-2-acetylpyrrole (**IV.15**, 75 mg, 0.358 mmol, 1 equiv) was added slowly. The reaction was stirred for another hour, was cooled to 0 °C and quenched with HCl/MeOH. This was extracted with ethyl acetate (10 mL, 3 xs). The organics were combined and dried with Na₂SO₄, and the solvent was removed under reduced pressure. Crude NMR showed no indication of starting material or the desired product.

2-Acetyl-*N*-methylpyrrole (**IV.16**): To a 25 mL round bottom flask, *N*-methylpyrrole (0.36 mL, 324.5 mg, 4 mmol, 1 equiv), acetylchloride (0.43 mL, 471 mg, 6 mmol, 1.5 equiv), Zn(OTf)₂ (145.4 mg, 0.4 mmol, 0.1 equiv) and nitromethane (5 mL) were added and stirred under N₂ for 4 hours. NaHCO₃ (aq sat, 10 mL) was added to quench. The aqueous layer was extracted with chloroform (20 mL, 3 xs). The organics were combined and dried with Na₂SO₄, and the solvent was removed under reduced pressure to provide the crude as a dark oil. The crude was purified by column chromatography (20% EtOAc/hexanes) and the product, **IV.16**, was isolated as a yellow oil (84 mg, 17%).

(**IV.16**): ¹H NMR (CDCl₃, 500 MHz): δ 6.92 (1H, dd, *J* = 4.0, 1.5 Hz), 6.77 (1H, t, *J* = 2.0 Hz), 6.10 (1H, dd, *J* = 4.5, 2.5 Hz), 3.91 (3H, s), 2.41 (3H, s).

Matches literature reported spectra.⁸²

1*R*-(*N*-methylpyrrolyl)-ethan-1-ol: 2-Acetyl-*N*-methylpyrrole (IV.16, 25 mg, 0.20 mmol, 1 equiv) and Ru(η^6 -mesitylene)-(*R,R*)-TsDPEN (Noyori's catalyst, 0.25 mol%, too small to measure, a small amount was added) were added to a 5 mL pear shaped flask containing formic acid:triethylamine (2:1 mol:mol, 0.2 mL). This was stirred for 24 hours under N₂. The reaction was quenched with H₂O (3 mL) and extracted with ethyl acetate (10 mL, 3 xs). The organic layers were combined and washed with NaHCO₃ (aq sat, 30 mL, 2 xs), brine (aq sat, 30 mL, 2 xs) and dried with Na₂SO₄. The solvent was removed under reduced pressure and crude NMR showed starting material with several unidentifiable decomposition products. There was no indication that the desired product had formed (no methyl doublet for the alcohol).

N-Tosylpyrrole-2-carboxaldehyde (IV.17): In a flame dried 50 mL round bottom flask, NaH (75 mg, 3.13 mmol, 1.2 equiv) and THF (15 mL) were added and the flask was flushed with Argon. To this flask, pyrrole-2-carboxaldehyde (250 mg, 2.75 mmol, 1 equiv) dissolved in THF (2.5 mL) was added dropwise. The suspension was stirred for an hour, to which tosyl chloride (550 mg, 3.03 mmol, 1.1 equiv) dissolved in THF (5 mL) was added. The reaction was stirred for 12 hours, and was quenched with NH₄Cl (sat. aq., 20 mL). The aqueous layer was extracted with EtOAc (30 mL, 3 xs) then the organics were combined, washed with NaCl (sat. aq., 30 mL) and dried with Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (50% EtOAc/hexanes). The desired product was isolated as a purple solid (552 mg, 80%).

(**IV.17**): ^1H NMR (CDCl_3 , 500 MHz): δ 9.96 (1H, s), 6.92 (1H, dd, J = 4.0, 1.5 Hz), 6.77 (1H, t, J = 2.0 Hz), 6.10 (1H, dd, J = 4.5, 2.5 Hz), 3.91 (3H, s), 2.40 (3H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 179.1, 145.95, 135.1, 133.7, 130.3, 129.8, 127.2, 122.2, 112.1, 21.9.

Mass Spectrum: $[\text{C}_{12}\text{H}_{12}\text{NO}_3\text{S}]^+$ observed 250.0 m/z calculated 250.1 m/z

Melting Point: 84- 86 $^\circ\text{C}$

Phenyl-(*N*-Tosyl-pyrrol-2-yl) methanol (**IV.18**): In a dry 50 mL round bottom flask, magnesium powder (51 mg, 2.1 mmol, 7 equiv) and iodine (1 crystal) were added to diethyl ether (2 mL). To this suspension, bromobenzene (160 μL , 235 mg, 1.5 mmol, 5 equiv) diluted with THF (3 mL) was added at room temperature. After 30 minutes, *N*-tosylpyrrole-2-carboxaldehyde (**IV.17**, 75 mg, 0.3 mmol, 1 equiv) was dissolved in THF (1 mL) and was added dropwise to the magnesium suspension. The reaction was monitored by TLC and was complete after 5 hours. The reaction was quenched with NH_4Cl (aq sat, 10 mL) and diluted with H_2O (100 mL). The aqueous layer was extracted with ethyl acetate (75 mL, 3 xs), and the organics were combined and dried with brine (100 mL) and Na_2SO_4 . The solvent was removed under reduced pressure and the crude was purified by column chromatography to provide the desired product (**IV.18**, 81 mg, 82%).

(**IV.18**): ^1H NMR (CDCl_3 , 500 MHz): δ 7.59 (2H, d, J = 8.5 Hz), 7.28 (1H, dd, J = 3.5, 2.0 Hz), 7.26 - 7.23 (7H, m), 6.15 (1H, t, J = 3.5 Hz), 6.05 (1H, d, J = 4.5 Hz), 5.77 (1H, m), 3.18 (1H, d, J = 4.5 Hz), 2.40 (3H, s).

^{13}C NMR (CDCl_3 , 125 MHz): δ 145.1, 140.8, 138.0, 136.1, 129.9, 128.1, 127.6, 126.65, 126.59, 123.8, 115.4, 111.5, 68.0, 21.6.

Mass Spectrum: $[\text{C}_{18}\text{H}_{18}\text{NO}_3\text{S}]^+$ observed 328.1 m/z calculated 328.1 m/z

1-(*N*-Tosyl-pyrrol-2-yl) ethan-1-ol (**IV.19**): In a dry 50 mL round bottom flask, magnesium powder (170 mg, 7 mmol, 7 equiv) and iodine (1 crystal) were added to diethyl ether (2 mL). To this suspension, bromomethane (150 μL , 495 mg, 5.2 mmol, 5.2 equiv) diluted with THF (3 mL) was added at room temperature. After 30 minutes, *N*-tosylpyrrole-2-carboxaldehyde (**IV.17**, 107 mg, 0.5 mmol, 1 equiv) was dissolved in THF (1 mL) and was added dropwise to the magnesium suspension. The reaction was monitored by TLC and was complete after 5 hours. The reaction was quenched with NH_4Cl (aq sat, 10 mL) and diluted with H_2O (100 mL). The aqueous layer was extracted with ethyl acetate (75 mL, 3 xs), and the organics were combined and dried with brine (100 mL) and Na_2SO_4 . The solvent was removed under reduced pressure and the crude was purified by column chromatography to provide the desired product (**IV.19**, 54 mg, 41%).

(**IV.19**): ^1H NMR (CDCl_3 , 500 MHz): δ 7.65 (2H, d, J = 8.5 Hz), 7.29 - 7.26 (3H, m), 6.27 (1H, m), 6.22 (1H, t, J = 2.5 Hz), 4.98 (1H, q, J = 7.0 Hz), 3.01 (1H, br s), 2.39 (3H, s), 1.47 (3H, d, J = 6.5 Hz).

^{13}C NMR (CDCl_3 , 125 MHz): δ 145.2, 138.9, 136.2, 130.1, 126.6, 123.5, 112.0, 111.5, 61.2, 21.6, 20.9.

Mass Spectrum: $[\text{C}_{13}\text{H}_{16}\text{NO}_3\text{S}]^+$ observed 266.1 m/z calculated 266.1 m/z

2-acetylfuran (**IV.20**): A: To a 100mL round bottom flask, furan (0.72 mL, 0.68 g, 10 mmol, 1 equiv), acetyl chloride (1.1 mL, 1.17 g, 15 mmol, 1.5 equiv), zinc dust (1.3 g, 20 mmol, 2 equiv) and toluene (20 mL, dry) were added. This suspension was stirred for 1 hour at room temperature and was quenched with NaHCO₃ (aq sat, 30 mL). The mixture was extracted with ethyl acetate (30 mL, 3 xs). The organics were combined and dried with Na₂SO₄, and the solvent was removed under reduced pressure to provide the crude as a dark oil. The crude was purified by column chromatography (10% EtOAc/hexanes). Even after purification, major impurities remained. This method was abandoned.¹⁰

B: To a 25 mL round bottom flask, furan (0.3 mL, 272.3 mg, 4 mmol, 1 equiv), acetylchloride (0.43 mL, 471 mg, 6 mmol, 1.5 equiv), Zn(OTf)₂ (45.4 mg, 0.4 mmol, 0.1 equiv) and nitromethane (5 mL) were added and stirred under N₂ for 4 hours. NaHCO₃ (aq sat, 10 mL) was added to quench. The aqueous layer was extracted with chloroform (20 mL, 3 xs). The organics were combined and dried with Na₂SO₄, and the solvent was removed under reduced pressure to provide the crude as a dark oil. The crude was purified by column chromatography (20% EtOAc/hexanes) and the product, IV.20, was isolated as a yellow oil (40 mg, 18%).

(**IV.20**): ¹H NMR (CDCl₃, 500 MHz): δ 7.55 (1H, m), 7.15 (1H, m), 6.51 (1H, m), 2.46 (3H, s).

Matches literature reported spectra.

(*R*)-1-(fur-2-yl)ethanol ((**R**)-**IV.21**): 2-acetylfuran (IV.20, 40 mg, 0.36 μmol, 1 equiv) and Ru(η⁶-mesitylene)-(*R,R*)-TsDPEN (Noyori's catalyst, 0.25 mol%, too small to measure, a small amount was added) were added to a 5 mL pear shaped flask containing formic acid:triethylamine (2:1 mol:mol, 1 mL). This was stirred for 24 hours under N₂. The reaction was quenched with H₂O

(3 mL) and extracted with ethyl acetate (10 mL, 3 xs). The organic layers were combined and washed with NaHCO₃ (aq sat, 30 mL, 2 xs), and brine (aq sat, 30 mL, 2 xs) and dried with Na₂SO₄. The solvent was removed under reduced pressure to give the crude alcohol. The crude was purified by column chromatography (50% EtOAc/hexanes) to give the desired product as a yellow oil (31 mg, 78%).

((R)-IV.21): ¹H NMR (CDCl₃, 500 MHz): δ 7.35 (1H, m), 6.30 (1H, m), 6.00 (1H, m), 4.8 (1H, m), 1.47 (3H, d, J = 5 Hz).

[α]_D (1 g/100 mL, 20 °C, CHCl₃) = +16.9 °, reported [α]_D (1 g/100 mL, 20 °C, CHCl₃) = +17.3 °
Matches literature reported spectra.⁸³

1-(fur-2-yl)hexanone (**IV.22**): In a dry 50 mL round bottom flask, *n*-pentylmagnesium bromide (2 M in diethyl ether, 1.5 mL, 3 mmol, 3 equiv) and diethyl ether (dry, 1.5 mL) were added under Argon and cooled to 0 °C. Furan-2-carboxaldehyde (0.08 mL, 96 mg, 1 mmol, 1 equiv) was dissolved in diethyl ether (dry, 1 mL) and was added dropwise to the Grignard solution. The reaction was monitored by TLC; after 5 hours, the reaction was quenched with NH₄Cl (aq sat, 10 mL) and diluted with H₂O (10 mL). The aqueous layer was extracted with ethyl acetate (20 mL, 3 xs), and the organics were combined and dried with brine (50 mL) and Na₂SO₄. The solvent was removed under reduced pressure and the crude was purified by column chromatography (5% EtOAc/hexane/1% Et₃N) to provide the desired product as yellow oil (165 mg, quantitative).

(1-(fur-2-yl)-hexan-1-ol): ¹H NMR (CDCl₃, 500 MHz): δ 7.35 (1H, m), 6.31 (1H, m), 6.21 (1H, m), 4.65 (1H, q, J = 6.5 Hz), 1.84-1.78 (3H, m), 1.42 (1H, m), 0.87 (3H, t, J = 6.5 Hz).

To a 50 mL round bottom flask, 1-(fur-2-yl)hexanol (50 mg, 0.29 mmol, 1 equiv) and manganese dioxide (517 mg, 5.9 mmol, 20 equiv) and CH₂Cl₂ (10 mL) were added and stirred for 48 hours at room temperature. The suspension was filtered through celite, the celite was rinsed with CH₂Cl₂, and the solvent was removed under reduced pressure to provide the crude product as a yellow oil. The crude was purified by column chromatography (5% EtOAc/hexanes/1% Et₃N) and the desired product was isolated as a clear oil (13 mg, 50% conversion, 34% BRSM).

(**IV.22**): ¹H NMR (CDCl₃, 500 MHz): δ 7.55 (1H, dd, *J* = 0.5, 1.5 Hz), 7.15 (1H, dd, *J* = 1.0, 4.0 Hz), 6.50 (1H, dd, *J* = 1.5, 3.5 Hz), 2.78 (1H, t, *J* = 7.5 Hz), 1.73-1.67 (2H, m), 1.35-1.31 (4H, m), 0.88 (3H, m).

¹³C NMR (CDCl₃, 125 MHz): δ 188.9, 141.4, 146.1, 116.8, 112.0, 38.2, 32.3, 23.8, 22.1, 13.98.

Mass Spectrum: [C₉H₁₇O₂]⁺ observed 167.1 m/z calculated 167.1 m/z

Matches literature reported spectra.⁸⁵

(*R*)-1-(fur-2-yl)-hexan-1-ol ((**R**)-**IV.23**): 1-(fur-2-yl)hexanone (IV.22, 25 mg, 0.15 mmol, 1 equiv) and Ru(η⁶-mesitylene)-(*R,R*)-TsDPEN (Noyori's catalyst, 0.25 mol%, too small to measure, a small amount was added) were added to a 5 mL pear shaped flask containing formic acid:triethylamine (2:1 mol:mol, 1 mL) CH₂Cl₂ (0.1 mL). This was stirred for 24 hours. The reaction was quenched with H₂O (3 mL) and extracted with ethyl acetate (10 mL, 3 xs). The organic layers were combined and washed with NaHCO₃ (aq sat, 30 mL, 2 xs), and brine (aq sat, 30 mL, 2 xs) and dried with Na₂SO₄. The solvent was removed under reduced pressure to

provide the crude alcohol. The crude was purified by column chromatography (5% EtOAc/hexanes) to give the desired product as a yellow oil (12 mg, 50%, >95% *ee*).

((R)-IV.23): ^1H NMR (CDCl_3 , 500 MHz): δ 7.35 (1H, m), 6.31 (1H, m), 6.21 (1H, m), 4.65 (1H, q, J = 6.5 Hz), 1.84-1.78 (3H, m), 1.42 (1H, m), 0.87 (3H, t, J = 6.5 Hz).

$[\alpha]_{\text{D}}$ (0.6 g/100 mL, 20 °C, CHCl_3) = +13.2 °, reported $[\alpha]_{\text{D}}$ (0.61 g/100 mL, 24 °C, CHCl_3) = +14.3 °

Matches literature reported spectra.⁸⁵

(*R*)-1-(thiophen-2-yl)ethanol (**((R)-IV.24)**): 2-acetylthiophene (126.2 mg, 0.1 mL, 1 mmol, 1 equiv) and $\text{Ru}(\eta^6\text{-mesitylene})\text{-(R,R)-TsDPEN}$ (Noyori's catalyst, 0.25 mol%, 1.5 mg) were added to a 5 mL pear shaped flask containing formic acid:triethylamine (2:1 mol:mol, 1 mL) and CH_2Cl_2 (0.2 mL). This was stirred for 24 hours. The reaction was quenched with H_2O (3 mL) and extracted with ethyl acetate (10 mL, 3 xs). The organic layers were combined and washed with NaHCO_3 (aq sat, 30 mL, 2 xs), and the brine (aq sat, 30 mL, 2 xs) and dried with Na_2SO_4 . The solvent was removed under reduced pressure to provide the crude alcohol. The crude was purified by column chromatography (25% EtOAc/hexanes) to give the desired product as a yellow oil (125 mg, quantitative, 96% *ee*).

((R)-IV.24): ^1H NMR (CDCl_3 , 500 MHz): δ 7.23 (1H, dd, J = 2.5, 7.5 Hz), 6.98-6.93 (2H, m), 5.12 (1H, m), 1.59 (3H, d, J = 10.0 Hz).

$[\alpha]_{\text{D}}$ (2.5 g/100 mL, 20 °C, CHCl_3) = +23.8 °, reported $[\alpha]_{\text{D}}$ (2.5 g/100 mL, 24 °C, CHCl_3) = +27 °

Matches literature reported spectra.⁸⁶

(S)-1-(*N*-methylpyrrol-2-yl)propan-2-ol ((S)-IV.25):

To a dry 50 mL round bottom under Ar at 0 °C, *N*-methylpyrrole (0.2 mL, 193 mg, 2.88 mmol, 1 equiv) was dissolved in diethyl ether (dry, 10 mL). TMEDA (0.412 mL, 319.6 mg, 2.75 mmol, 1 equiv) was added followed by *n*-BuLi (1.6 M in hexanes, 1.72 mL, 2.75 mmol, 1 equiv). This mixture was slowly warmed to room temperature and stirred for 2 hours. The reaction was chilled again to 0 °C and (S)-(-)-propylene oxide (0.17 mL, 143.7 mg, 2.48 mmol, 0.9 equiv) was added. Again the reaction was slowly warmed to room temperature and was monitored by TLC. When the epoxide was no longer detected by TLC, about 3 hours, the reaction was quenched by pouring over ice water. The aqueous solution was extracted with ethyl acetate (20 mL, 3 xs) and the organics were combined. The organic was washed with NaHCO₃ (aq sat, 40 mL, 2 xs) and dried with Na₂SO₄. The solvent was removed under reduced pressure to give the crude, which was purified by column chromatography (10% EtOAc/hexanes - 50% EtOAc/hexanes). The desired product was isolated as a yellow oil (170 mg, 47%).

((S)-IV.25): ¹H NMR (CDCl₃, 500 MHz): δ 6.55 (1H, m), 6.06 (1H, t, J = 3.5), 5.97-5.95 (1H, m), 3.96 (1H, m), 3.55 (3H, s), 2.76-2.72 (1H, dd, J = 4, 15 Hz), 2.64-2.59 (1H, dd, J = 8.5, 14.5 Hz), 1.25 (3H, d, J = 6.5 Hz).

¹³C NMR (CDCl₃, 125 MHz): δ 129.2, 121.9, 106.8, 107.1, 66.7, 35.98, 33.8, 22.1.

Mass Spectrum: [C₈H₁₄NO]⁺ observed 140.1 m/z calculated 140.1 m/z

(*R*)-1-(*N*-methylpyrrol-2-yl)propan-2-ol (**(*R*)-IV.25**): To a dry 50 mL round bottom under Ar at 0 °C, *N*-methylpyrrole (0.2 mL, 193 mg, 2.88 mmol, 1 equiv) was dissolved in diethyl ether (dry, 10 mL). TMEDA (0.412 mL, 319.6 mg, 2.75 mmol, 1 equiv) was added followed by *n*BuLi (1.6 M in hexanes, 1.72 mL, 2.75 mmol, 1 equiv). This mixture was slowly warmed to room temperature and stirred for 2 hours. The reaction was chilled again to 0 °C and (*R*)-(+)-propylene oxide (0.17 mL, 143.7 mg, 2.48 mmol, 0.9 equiv) was added. Again the reaction was slowly warmed to room temperature and was monitored by TLC. When the epoxide was no longer detected by TLC, about 3 hours, the reaction was quenched by pouring over ice water. The aqueous solution was extracted with ethyl acetate (20 mL, 3 xs) and the organics were combined. The organic was washed with NaHCO₃ (aq sat, 40 mL, 2 xs) and dried with Na₂SO₄. The solvent was removed under reduced pressure to give the crude, which was purified by column chromatography (10% EtOAc/hexanes - 50% EtOAc/hexanes). The desired product was isolated as a yellow oil (170 mg, 47%).

(*R*)-IV.25: ¹H NMR (CDCl₃, 500 MHz): δ 6.55 (1H, m), 6.06 (1H, t, *J* = 3.5 Hz), 5.97-5.95 (1H, m), 3.96 (1H, m), 3.55 (3H, s), 2.76-2.72 (1H, dd, *J* = 4.0, 15.0 Hz), 2.64-2.59 (1H, dd, *J* = 8.5, 14.5 Hz), 1.25 (3H, d, *J* = 6.5 Hz).

¹³C NMR (CDCl₃, 125 MHz): δ 129.3, 121.9, 106.8, 107.1, 66.8, 35.98, 33.8, 22.2.

Mass Spectrum: [C₈H₁₄NO]⁺ observed 140.1 m/z calculated 140.1 m/z

(S)-1-(fur-2-yl)propan-2-ol (**(S)-IV.26**): To a dry 50 mL round bottom under Ar at 0 °C, furan (0.2 mL, 187 mg, 2.75 mmol, 1 equiv) was dissolved in diethyl ether (dry, 10 mL). TMEDA (0.41 mL, 320 mg, 2.75 mmol, 1 equiv) was added followed by *n*-BuLi (1.2 M in hexanes, 4 mL, 4.8 mmol, 1.7 equiv). This mixture was slowly warmed to room temperature and stirred for 2 hours. The reaction was chilled again to 0 °C and (S)-(-)-propylene oxide (0.5 mL, 414.5 mg, 7.1 mmol, 2.6 equiv) was added. Again the reaction was slowly warmed to room temperature and was monitored by TLC. When the epoxide was no longer detected by TLC, about 3 hours, the reaction was quenched by pouring over ice water. The aqueous solution was extracted with ethyl acetate (20 mL, 3 xs) and the organics were combined. The organic was washed with NaHCO₃ (aq sat, 40 mL, 2 xs) and dried with Na₂SO₄. The solvent was removed under reduced pressure to give the crude which was purified by column chromatography (10% EtOAc/hexanes - 50% EtOAc/hexanes). The desired product was isolated as a yellow oil (40 mg, 32%).

(S)-IV.26: ¹H NMR (CDCl₃, 300 MHz): δ 7.32 (1H, dd, J = 1.8, 0.9 Hz), 6.29 (1H, m), 6.09 (1H, m), 4.09 (1H, m), 2.83 - 2.68 (2H, m), 1.11 (3H, d, J = 6.9 Hz).

Matches literature reported spectra.⁸⁸

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Chapter V

Determination of Absolute Stereochemistry for Chiral Epoxy and Aziridine Amides

V.1: Background

Aziridines and epoxides are three member rings that contain nitrogen and oxygen, respectively, within the cycle (Figure V.1, highlighted in blue). These functionalities are found in several important classes of biologically active molecules and serve as important building blocks to more complex amines, alcohols and ethers. One such class of biologically important aziridines, mitomycins, were first isolated in 1958 and have been a challenge for synthetic chemists over the last 60 years. The biological activity of mitomycins against non-small-cell

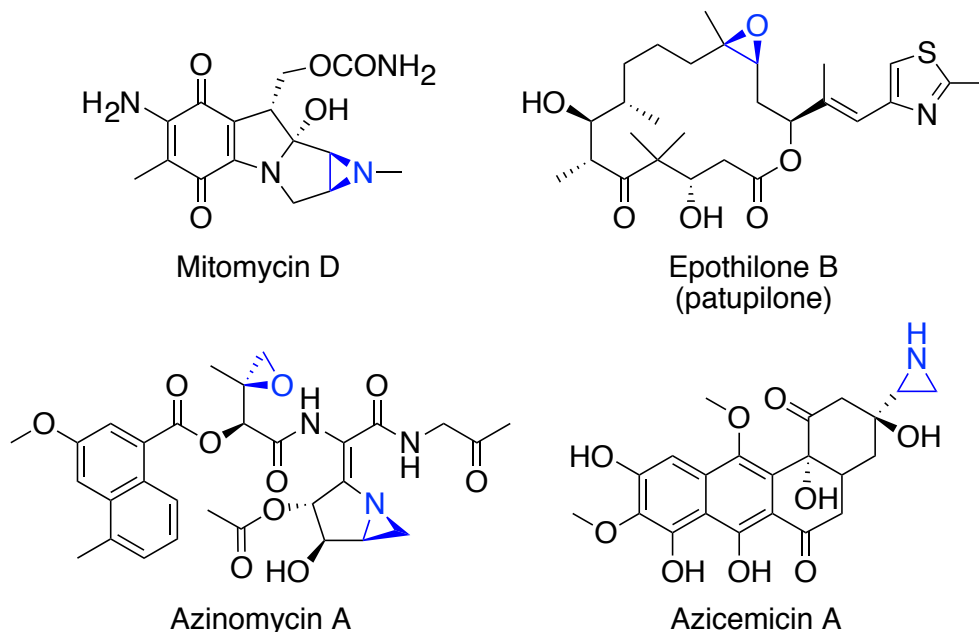


Figure V.1: Structures of selected biologically active molecules containing aziridine and/or epoxide functionalities (highlighted in blue).¹⁻³

lung carcinomas originates from the aziridine which is opened to serve as an electrophilic site during DNA alkylation.¹ The epoxide based family of biologically active molecules, epithilones, have shown activity against a range of cancer cell lines.² These molecules are known to bind to β -tubulin causing tubulin polymerization and preventing tubulin depolymerization thereby causing the cell to undergo apoptosis. Other aziridine and epoxide containing molecules have also shown biological activity which is initiated from the three member ring.¹⁻³

These motifs are often exploited for their unique reactivity, serving as chiral building blocks to molecules of greater structural complexity. The strained three member ring has been described as “spring-loaded” for ring opening by nucleophilic attack.⁴ A number of nucleophiles are known to open aziridines and epoxides granting access to amines and alcohols.⁴⁻⁷ Furthermore, ring expansion reactions provide access to any number of larger heterocycles containing an amine or ether.⁸⁻¹² Additionally, epoxides and aziridines are utilized in the synthesis of bulk chemicals such as polyethylenimine and ethylene glycol. Thus, these are important molecules for industry and pharmaceuticals.

With the importance of aziridines and epoxides, there has been an increasing number of methodologies to access these scaffolds both racemically and asymmetrically. The Jacobsen-Katsuki epoxidation using a chiral manganese-salen complex,¹³⁻¹⁸ the Sharpless epoxidation featuring a titanium-tartrate complex¹⁹⁻²¹ and the Shi epoxidation with a fructose derived catalyst with oxone as the oxidant²²⁻²⁴ are arguably the most well established methodologies for the asymmetric synthesis of epoxides. As for synthesis of chiral aziridines, copper catalyzed methodologies from the Evans²⁵ and Jacobsen²⁶ groups, the Wulff aziridination using boron-VAPOL or VANOL complexes²⁷⁻³⁰ and the rhodium catalyzed aziridination featuring chiral

sulfide ligands reported by Aggarwal group³¹⁻³³ are well known. For these methodologies, the stereochemistry of the resulting aziridine or epoxide is determined by the established mnemonic. Even with the continual improvement of existing methodologies and disclosure of new methodologies, there are still few methodologies to non-empirically assign the absolute configuration of these three member rings.

V.2: Conventional Methods of Determining Chirality for Epoxides and Aziridines

As discussed above, the stereochemistry of a synthesized aziridine or epoxide can be predicted based on the mnemonic for the methodology in use. For example, studies of the Sharpless asymmetric epoxidation have elucidated a bis-titanium-tartrate complex that dictates the stereochemistry of the resulting epoxide.^{19,34} For predicting the the stereochemistry of

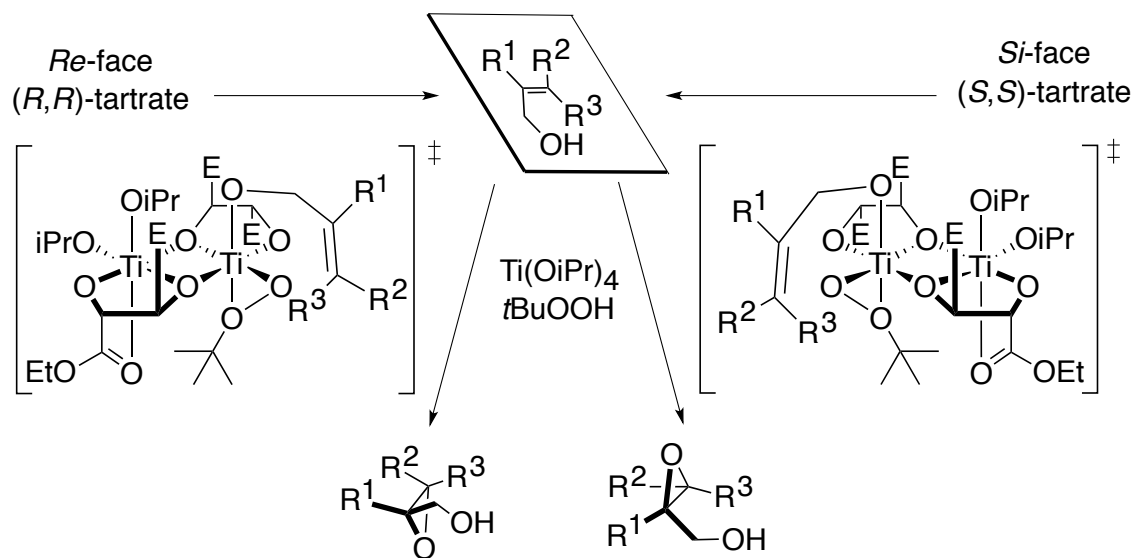


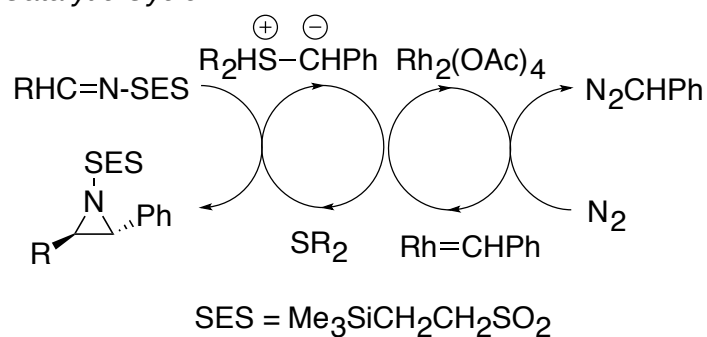
Figure V.2: Mnemonic for the Sharpless asymmetric epoxidation. Shown is the preferred face for oxygen addition based on the tartrate stereochemistry and the corresponding bis-titanium transition state complexes.^{19,34}

the epoxide, the alkene is aligned in a plane such that the alcohol lies in the bottom right hand corner of the plane (Figure V.2). When (*R,R*)-tartrate is used as the chiral ligand, the epoxide adds to the *Re* face of the pro-chiral epoxide. The (*S,S*)-tartrate favors addition of the oxygen to the *Si* face of the olefin.

As for the aziridination methodology developed by Aggarwal and coworkers, the configuration of the aziridine is dictated by the stereochemistry of the sulfonium ylide (Figure V.3).^{32,35} The aziridine is formed by the addition of the ylide carbon across an imine double bond. Formation of the ylide is generated by rhodium catalyzed addition of a carbene to a chiral thioacetal ligand. The preferred conformation of the ylide places the phenyl substituent equatorial to reduce A^{1,3} interactions (Figure V.3 B). The attack of the ylide onto the imine can occur to the *Re* (a, green arrow) or *Si* face (b, blue arrow). Attack to the *Si* face is hindered by the methyl group of the sulfonium. Being that *trans* aziridines are favored, the imine approaches the ylide to form the (*R,R*)-aziridine. The other chiral aziridinations and epoxidations have similar models for the prediction of the stereochemistry for the resulting aziridines and epoxides.

When the aziridine or epoxide is of unknown configuration, say part of a natural product, assignment of configuration is typically achieved by X-ray crystallography,³⁶ comparison of a ring opened product to an amine or alcohol of known configuration or NMR assignment based on coupling constants³⁷ or Mosher ester methodologies.³⁷ For natural products, comparison of the NMR spectra for the isolated sample with spectra for a synthesized sample has also been shown effective.³⁸ All of these methods require milligram quantities of

A: Catalytic Cycle



B: Origin of Enantioselectivity

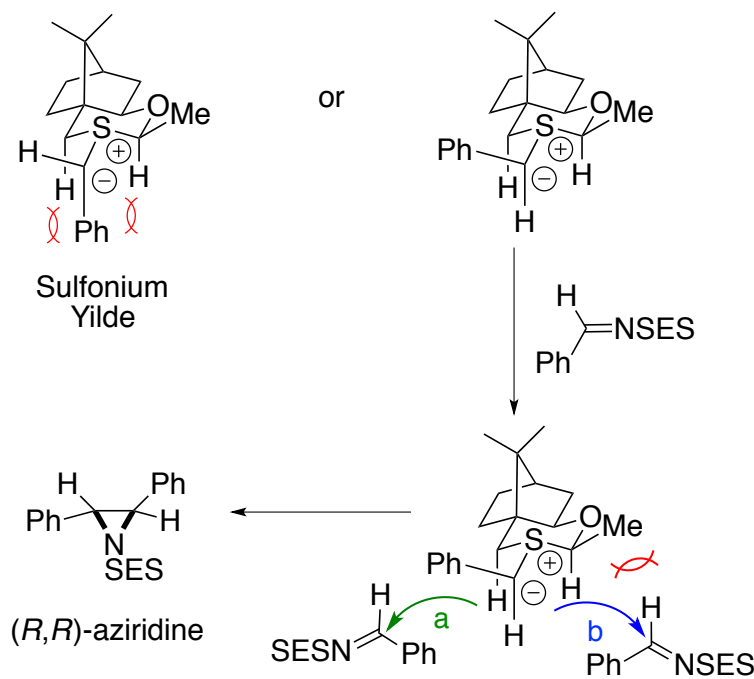


Figure V.3: Rhodium catalyzed sulfonium ylide chiral aziridination reported by Aggarwal and coworkers. **A:** The catalytic cycle **B:** The proposed origin of enantioselectivity. The sulfonium ylide favors the equatorial phenyl substituent to reduce $A^{1,3}$ strain. Addition of the imine to the ylide can occur to the *Re* face (a, green arrow) or *Si* face (b, blue arrow). Attack to the *Si* face is hindered due to steric interaction between the imine and Me of the sulfonium. Formation of the *trans* aziridine is favored thus, this ligand generates *(R,R)*-aziridines.^{32,35}

substrate for crystallization or chemical transformation. Furthermore, total synthesis can be time consuming and requires confirmation of stereochemistry through out the synthesis.

There are examples of chiroptical analysis of stereochemistry for aziridines and epoxides. ECD or VCD spectra for an unknown molecule can be obtained and compared to a calculated spectra.^{39,40} Alternatively, a model substrate could be synthesized and a comparison of the CD spectrum for the known molecule with the unknown aziridine or epoxide can be used to establish absolute configuration.⁴¹

An ECCD protocol using the Zn-TPFP-Tweezer for the determination of configuration for a variety of epoxy alcohols has been disclosed by our lab.⁴² The protocol established for *cis* and *trans* epoxy alcohols is summarized in the following. Dr. Xiaoyong Li demonstrated that the formation of a host-guest complex of C5-Zn-TPFP-Tweezer with an epoxy alcohol would produce an ECCD signal. The sign of this signal could then be directly correlated to the configuration of the epoxide. For *cis*-epoxides, the mnemonic describes porphyrin, P2, approaching the lone pair electrons of the epoxide that are located on the opposite face of the epoxide as the two carbon substituents. Being that two hydrogens face this porphyrin, no stereodifferentiation occurs. Porphyrin, P1, will approach the epoxide from the opposite face of P2 to minimize porphyrin-porphyrin interactions to bind with the oxygen of the hydroxyl. This porphyrin then rotates away from the substituent at the other carbon of the epoxide which induces the helical chirality into the tweezer. The linker of the porphyrin wraps under the oxygen of the epoxide rather than under the carbons of the epoxide. The example in Figure V. 4, an (*R,S*) epoxide, is predicted to generate a positive ECCD signal and the enantiomers would give a negative ECCD signal.

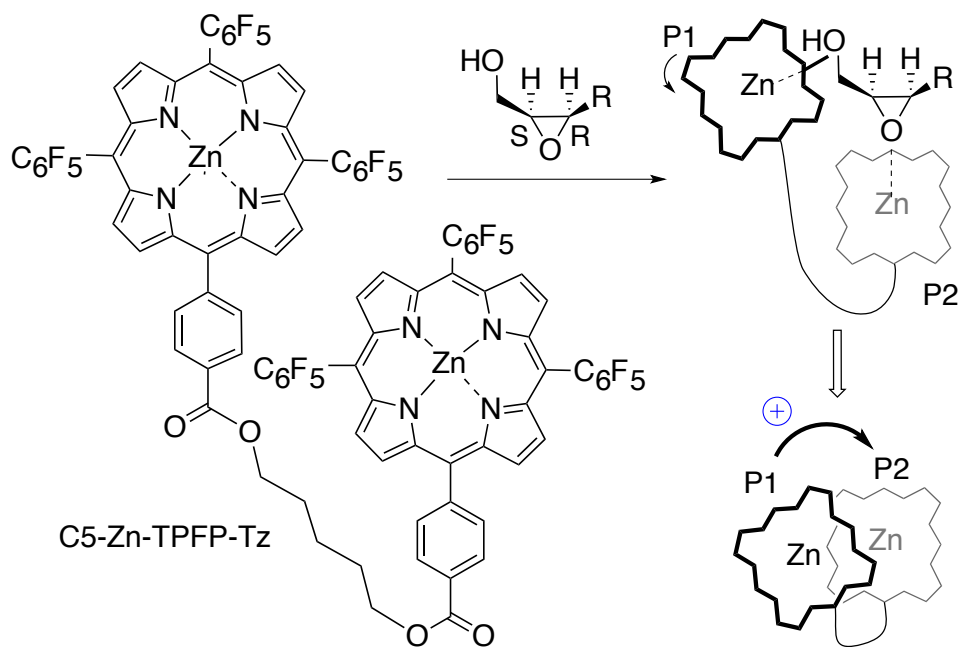


Figure V.4: Model for ECCD of *cis*-epoxides. The (*S,R*)-epoxide is expected to give a negative ECCD signal. P2 binds to the lone pair electrons to the back face of the epoxide oxygen, opposite of the hydroxyl substituent. P1 coordinates to the hydroxyl from the front face of the epoxide to reduce porphyrin-porphyrin interactions. This porphyrin rotates away from the R group to minimize sterics. A clockwise rotation from P1 to P2 is generated and a positive ECCD is expected.⁴²

Additionally, 1,1-disubstituted, *trans*-disubstituted and trisubstituted epoxides were evaluated. For the *trans* epoxides, the rationale for the observed ECCD sign is as follows. The porphyrin, P2, approaches the epoxide to the same face as the hydroxyl. For the (*S,S*) epoxide shown in Figure V.5, P2 approaches from to the back face of the epoxide. Then P1 binds to the opposite face of P2 to minimize the porphyrin-porphyrin interactions. On this face of the epoxide, there is an R group and a hydrogen atom. The porphyrin rotates away from the R group, toward the hydrogen. The relative orientation of P1 to P2 dictates the sign of the ECCD

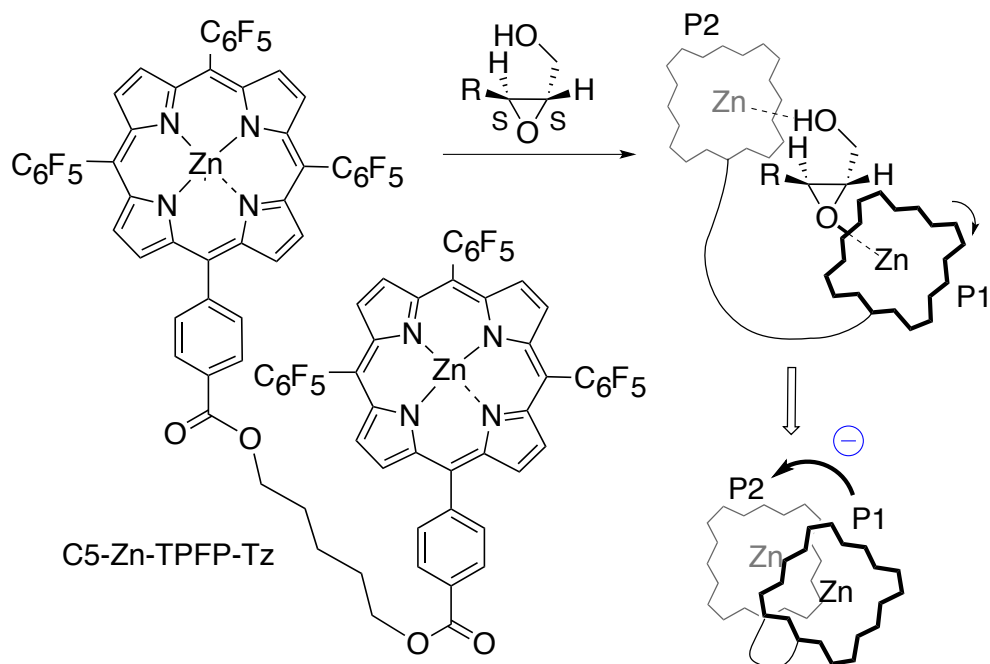


Figure V.5: Model for ECCD of *trans*-epoxides. The (*S,S*)-epoxide is expected to give a negative ECCD signal. P2 binds to the back face of the epoxide, where the hydroxyl substituent is situated. P1 coordinates to the epoxide oxygen from the front face of the epoxide to reduce porphyrin-porphyrin interactions. This porphyrin rotates away from the R group to minimize sterics. A clockwise rotation from P1 to P2 is generated and a positive ECCD is expected.⁴²

signal. The example in Figure V.5 is expected to generate a negative sign and the enantiomer would provide a positive ECCD.

V.3: ECCD Study of Chiral Aziridines

The study of chiral aziridines was initiated by Dr. Li after completion of his study on chiral epoxides.⁴³ It was already known that amines have higher binding affinity for the zinc center of the TFPF porphyrin than do oxygen functionalities and with the successful binding of

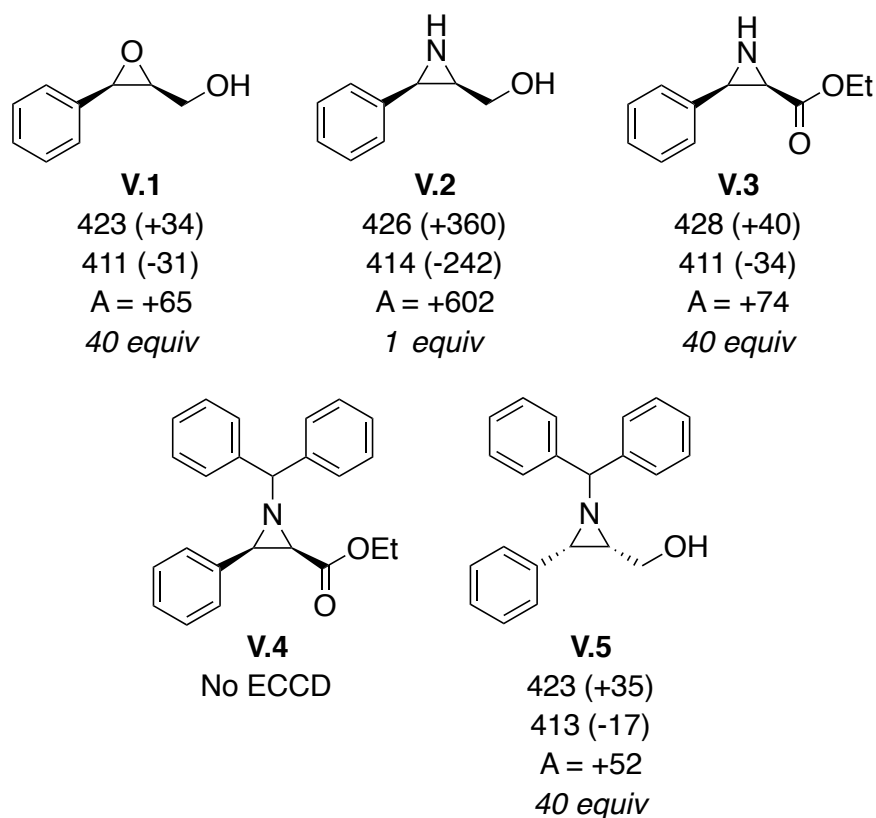


Figure V.6: ECCD results for *cis*-epoxy alcohols and *cis*-aziridines. All measurements: 2 μ M tweezer, hexanes, 0 °C. The equivalents of substrate is indicated.⁴³

the epoxide oxygen with the Zn-TPFP-Tweezer, Dr. Li hypothesized that nitrogen of an aziridine should also bind with the tweezer. A selection of *N*-protected-*cis*-aziridine esters were generously provided by Dr. Aman Desai from Professor Wulff's lab. The ECCD study of these aziridines lead to the development of a TPFP-Tweezer based mnemonic for *cis*-aziridines (Figure V.6). Initially, the *N*-protected-*cis*-aziridine esters were reduced then deprotected to generate the free *cis*-aziridine alcohols. It was thought that the sign of the ECCD signal for the free *cis*-aziridine alcohols could be predicted by the mnemonic established for the *cis*-epoxy alcohols as the binding mode and stereodifferentiation process should be the same for both classes of compounds (Figure V.7 A and B). Figure V.7 B summarizes the binding model for free *cis*-

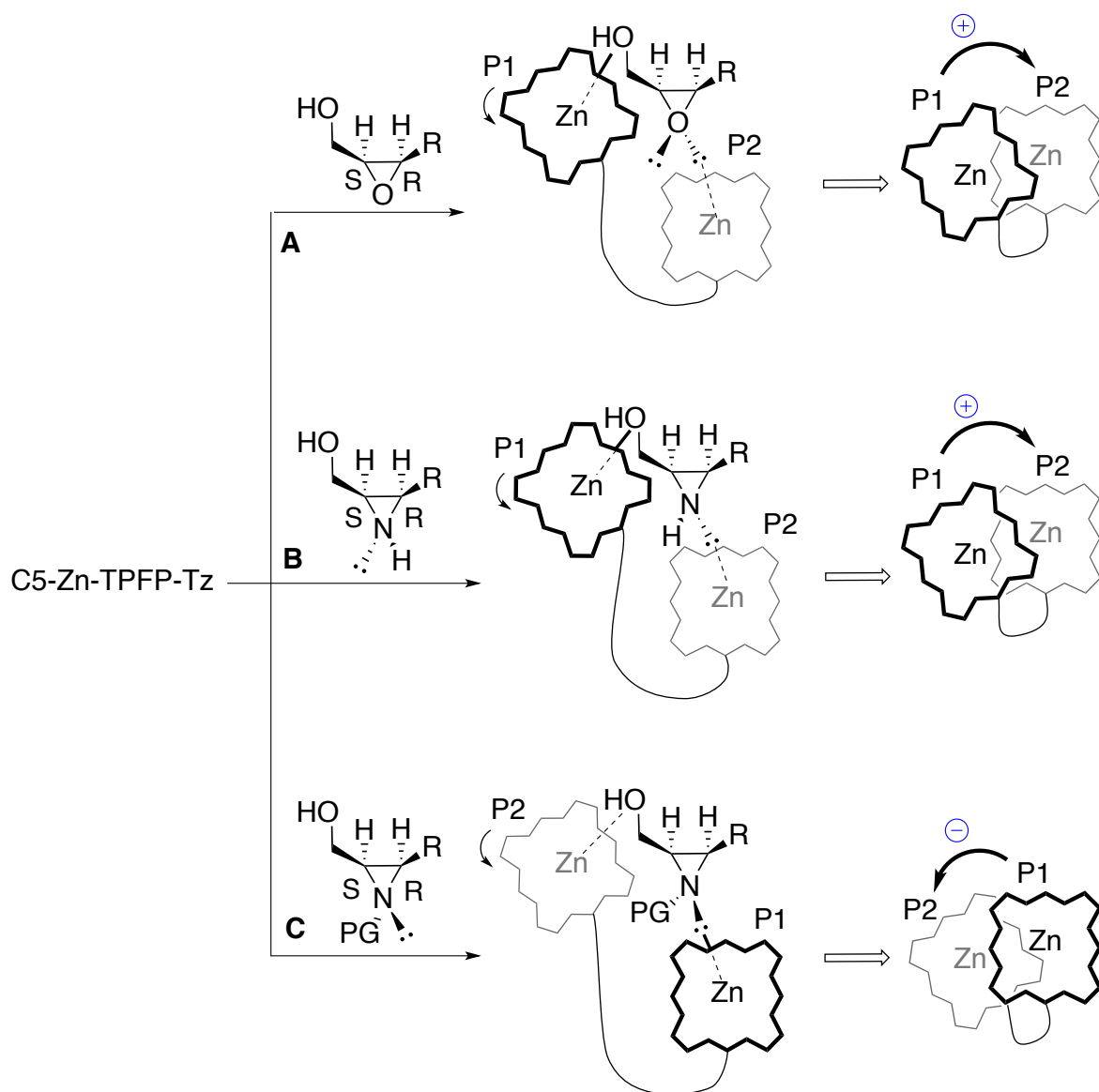


Figure V.7: Comparison of ECCD binding models for *cis*-epoxy and *cis*-aziridine alcohols.

A: Binding model for *cis*-epoxy alcohols **B:** Binding model for free *cis*-aziridines alcohols, which is analogous to the binding model for *cis*-epoxy alcohols. **C:** Binding model for *N*-protected-*cis*-aziridines alcohols. Pyramidalization of the nitrogen favors placement of the protecting group to the opposite face of the aziridine substituents. The change in pyramidalization inverts the helicity of the porphyrins in the complex which would result in an ECCD of opposite sign.

aziridines alcohols. The tweezer will bind with the conformer of the aziridine that situates the lone pair electrons of the nitrogen to the face of the aziridine opposite that of the alcohol. Porphyrin, P1, binds to the nitrogen and remains static as no steric differentiation will occur between the two hydrogens. Porphyrin, P2, binds to the alcohol from the opposite face as P1 to avoid porphyrin-porphyrin interaction. Rotation of P2 away from the bulky substituent of the aziridine results in the overall helicity of the porphyrins. As predicted, (2*S*, 3*R*)-3-phenyl-2,3-epoxypropan-1-ol and the analogous aziridine, (2*R*, 3*R*)-3-phenyl-2,3-aziridinylpropan-1-ol provided ECCD signals of the same sign (Figure V.6, substrates **V.1** and **V.2**). The amplitude for the aziridine was 10 times larger and required fewer equivalents of the substrate owing to the larger binding affinity for the aziridine to the zinc porphyrin.

Next, ECCD of the free *cis*-aziridine esters was attempted (Figure V.6, substrate **V.3**). Again, the sign of the ECCD signal could be predicted by the epoxy alcohol mnemonic, suggesting that these substrates share the same binding mode and process for transfer of chirality. The successful binding of the aziridine esters is attributed to cooperative binding. Small binding affinities between esters and the TPFP-Tweezer due to the weak Lewis basicity of the ester carbonyl has been observed in the past. But, the tight coordination of the aziridine nitrogen promotes binding with the ester through proximity effects. For these substrates, the ECCD amplitudes drop, which is likely due to the weak coordination of the ester.

Finally, extension of the methodology to include the *N*-protected-*cis*-aziridines was desired. Unfortunately, no ECCD signal was observed upon addition of an *N*-protected-*cis*-aziridine ester to the C5-Zn-TPFP-Tweezer. Yet, *N*-protected-*cis*-aziridine alcohols did generate ECCD signal (Figure V.6, substrates **V.4** and **V.5**). The lack of ECCD for *N*-protected-*cis*-aziridine

esters, is rationalized as a result of having two weakly binding functionalities as the protecting group of the nitrogen would inhibit binding of the nitrogen. With two weakly coordinating functionalities, either the host-guest complex does not form or the complex samples a number of ECCD active complexes that would generate ECCD signals of opposite signs. The summation of these signs results in unobservable ECCD.

Fortunately, alcohol functionalities exhibit tighter binding to the Zn-TPFP-Tweezer than do esters thus, ECCD signals are observed for *N*-protected-*cis*-aziridine alcohols. The sign of the ECCD signal for *N*-protected-*cis*-aziridine alcohols was opposite of the sign predicted by the epoxy alcohol mnemonic. The switch of sign has been attributed to a change of the preferred pyramidalization of the nitrogen due to the substituents of the aziridine and the protecting group of the nitrogen. The bulky protecting group will preferentially reside to the face of the aziridine opposite that of the aziridine substituents. As a result, the lone pair electrons of the nitrogen that are utilized for binding with the tweezer are flipped to the same face of the aziridine as the carbon substituents. The binding model for *N*-protected-*cis*-aziridine alcohols is shown in Figure V.7 C. The host-guest complex forms by binding of the nitrogen with P1 which will remain static as little differentiation is expected between two carbon based substituents. Then P2 approaches the alcohol from the opposite face of P1 to reduce porphyrin-porphyrin interactions. Rotation of P2 away from the aziridine results in the overall helicity of the porphyrins and subsequently the ECCD signal. The reduced binding affinity for the *N*-protected-*cis*-aziridine alcohols is thought to be largely a result of weak binding to the aziridine nitrogen due to the steric interactions with the substituents of the aziridine. In all, 11 chiral aziridines

were evaluated by ECCD. The sign of the ECCD signals for each substrate matched the predicted sign from the proposed binding mnemonic.

V.3.1: ECCD Study of *cis*-Aziridine Amides

Recently, the Wulff group has extended their aziridination methodology to access *cis*-aziridine amides. Unlike an ester functionality, binding of the amide functionality to the Zn-TPP-Tweezer was known through previous work on developing an ECCD protocol for the determination of absolute stereochemistry of chiral carboxylic acids.^{44,45} Therefore, ECCD of the *N*-protected aziridine amide was attempted without prior chemical modification. Being that C5-Zn-TPFP-Tweezer was shown to provide consistent and reliable results for the previously studied aziridines, this tweezer was chosen for ECCD analysis of the aziridine amides.

Figure V.8 summarizes the results of the ECCD study with *N*-protected aziridine amides. Fortunately, the three substrates of (*S,S*) configuration all provided negative ECCD and the psuedo-enantiomeric (*R,R*) aziridines generated positive ECCD. A signal was observed with as little as 0.2 equivalents of substrate indicating a tight binding of these substrates with the tweezer. Delightfully, ECCD was observed for **V.11**, a substrate with marginal enantiomeric excess.

UV-Vis analysis of each complex was also conducted. For substrate **V.9** (Figure V.9 B), the porphyrin Soret band shifts approximately 7 nm suggesting that a 1:1 tweezer-substrate complex has formed as the shift of the Soret band is smaller than the shift observed for addition of an amine (sec-butyl amine shifts to 424 nm, See Chapter 2 for a discussion on Soret band shifts and complex formation). Job's plot analysis with substrate **V.9** confirms that a 1:1

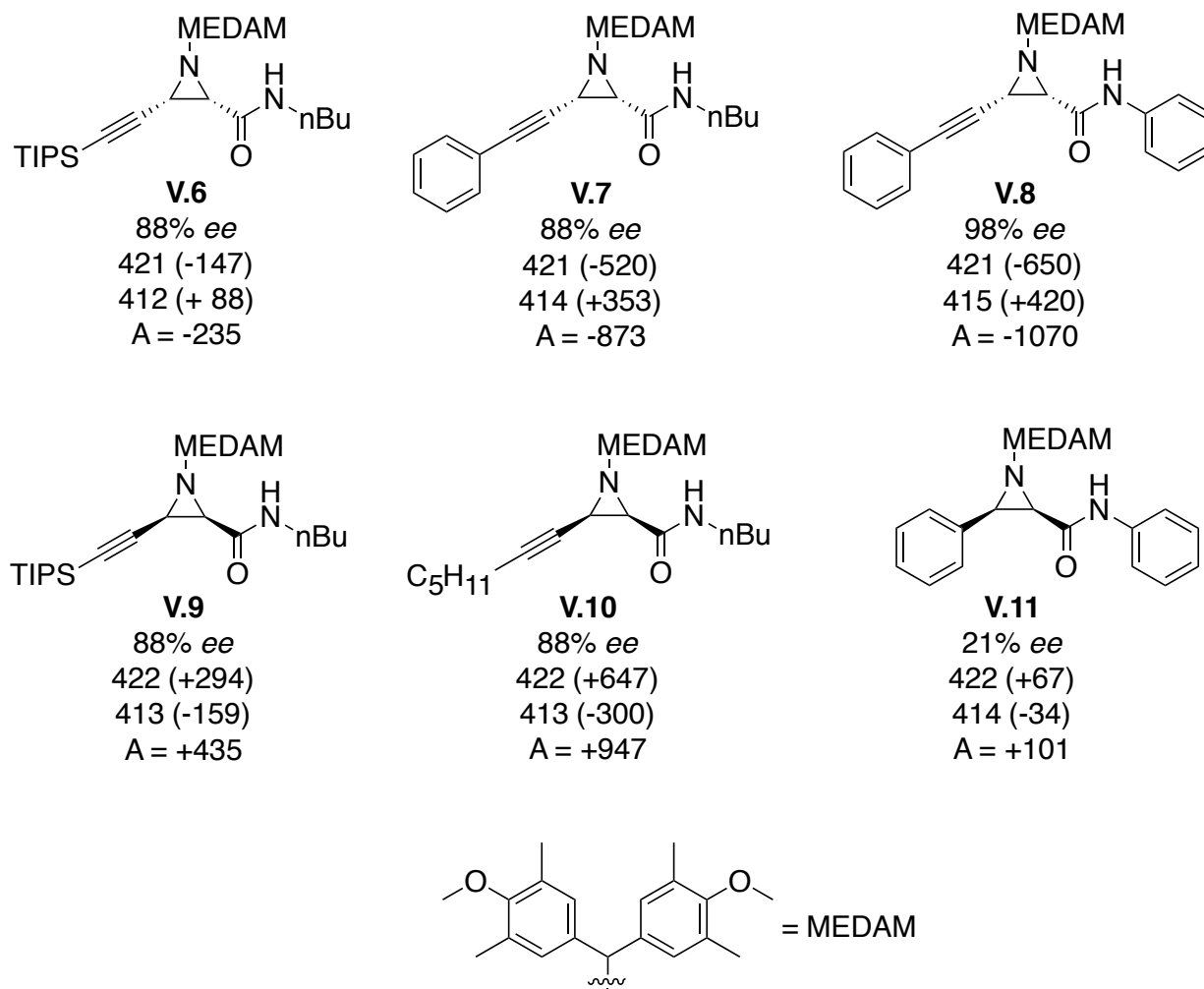


Figure V.8: ECCD results for *N*-MEDAM-*cis*-aziridine amides. All measurements: 2 μ M tweezer, hexanes, 0 $^{\circ}$ C, 10 equivalents of substrate.

complex tweezer-substrate was formed (Figure V.9 C). Finally, UV-Vis analysis allowed for the determination of the binding constant for substrate **V.9** which was calculated to be $3 \times 10^5 \text{ M}^{-1}$ (Figure V.9 D). This is smaller than the binding constant for an amine to Zn-TPFP-Me Ester (10^6 M^{-1}). This is likely a consequence of the nitrogen protecting group forcing the porphyrin to bind to the more hindered face of the aziridine and binding with the carbonyl of the amide, a weaker binding functionality.

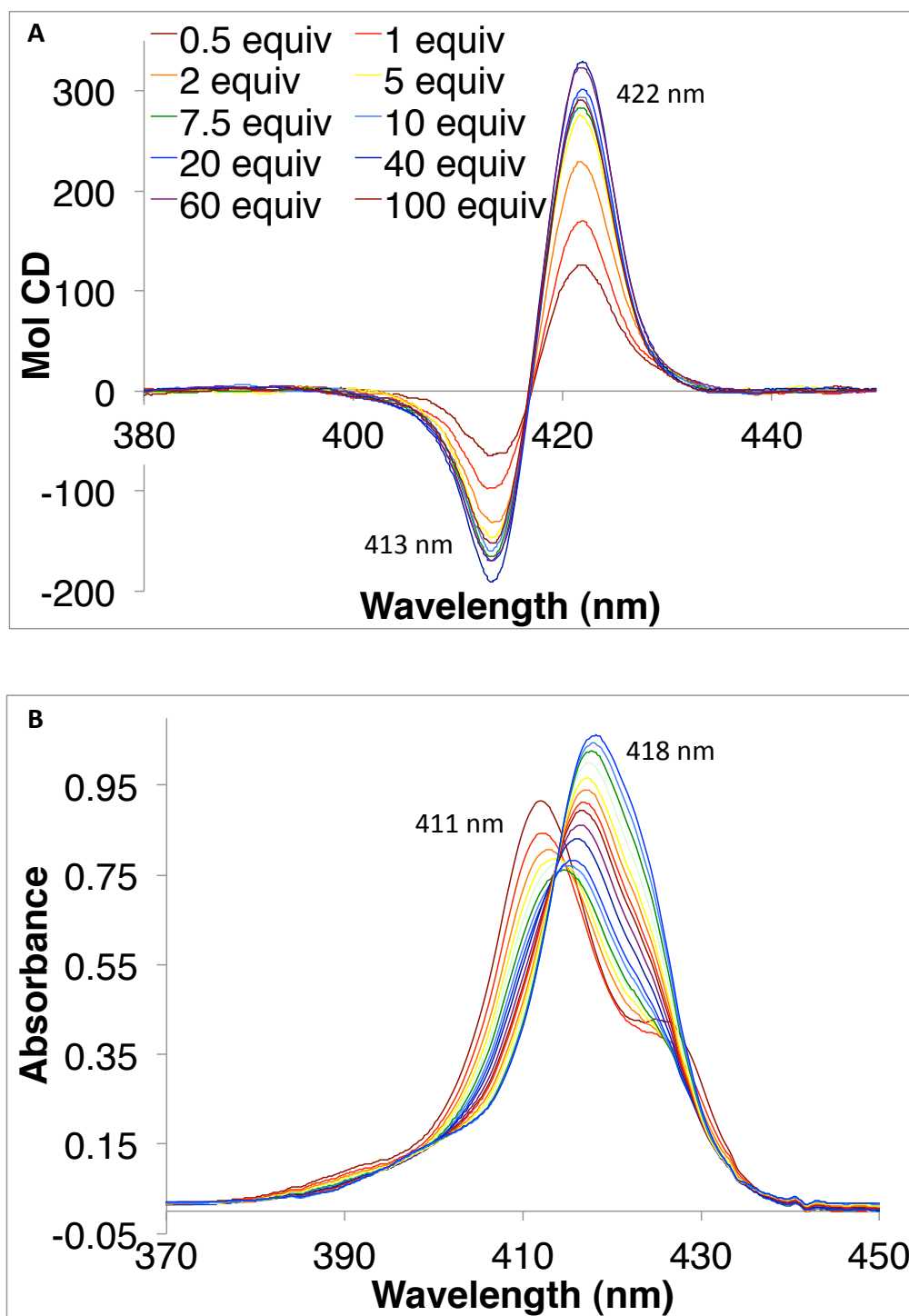


Figure V.9: Analysis of the C5-Zn-TPFP-Tz and **V.9** complex. **A:** ECD titration 2 μM Tz, hexanes, 0 $^{\circ}\text{C}$. **B:** UV-Vis titration 1 μM Tz, hexanes, room temperature.

Figure V.9 (cont'd): Analysis of the C5-Zn-TPFP-Tz and **V.9** complex. **C:** Job's plot analysis and **D:** Binding constant calculation. 1 μ M Tz, hexanes, room temperature

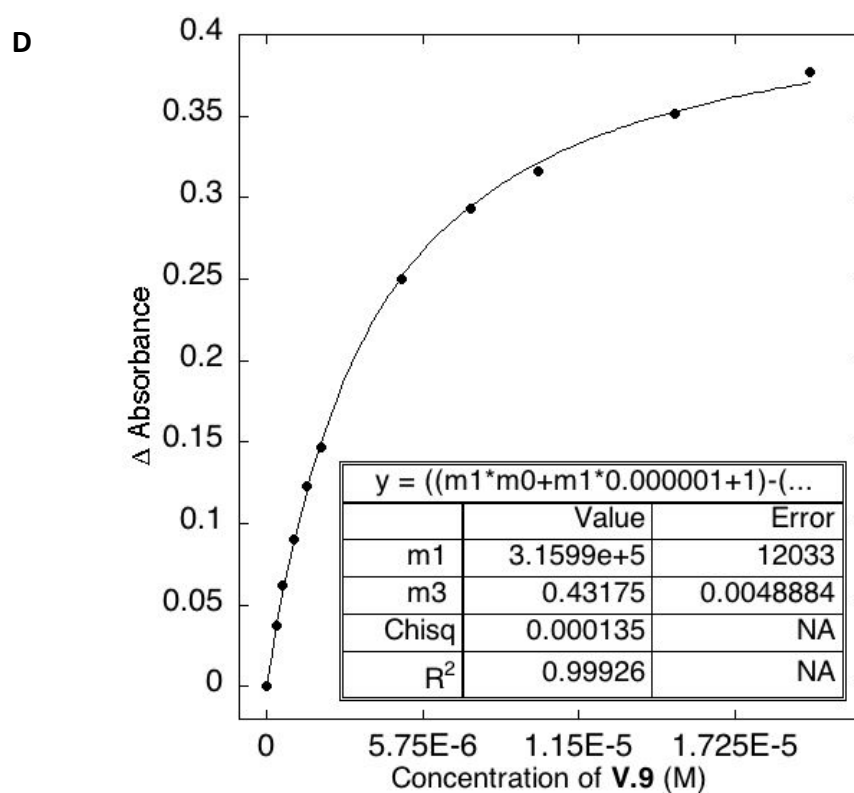
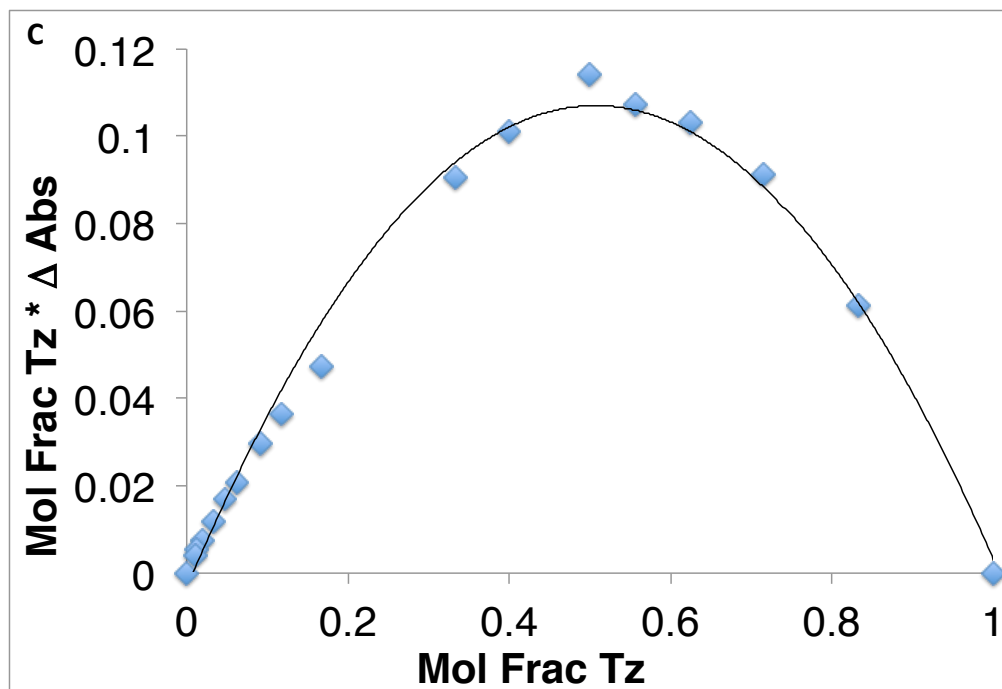


Figure V.10 summarizes the mnemonic proposed for the *N*-protected-*cis*-aziridine amides. In a similar fashion as the *N*-protected aziridine alcohols, the protecting group of the nitrogen will be found on the same face of the aziridine as the two hydrogen substituents to reduce steric interactions. This forces the lone pair electrons of the nitrogen to the more sterically hindered face of the aziridine. The porphyrin, P1, will coordinate with these electrons. The second porphyrin, P2, approaches the amide functionality from the opposite face of porphyrin P1 to avoid porphyrin-porphyrin interactions. Furthermore, the second porphyrin binds such that the linker wraps under through the carbons of the aziridine. If the

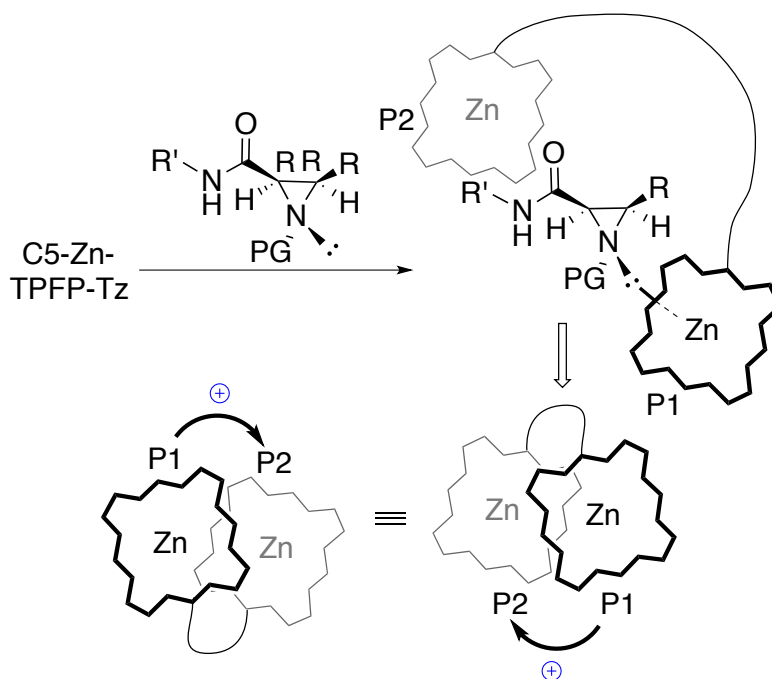


Figure V.10: ECCD model for *N*-protected-*cis*-aziridine amides. The model for (*R,R*) configured aziridine amides is shown. Pyramidalization of the nitrogen favors placement of the protecting group to the opposite face of the aziridine substituents. Minimization of steric factors results in the helicity of the porphyrins and the expected sign of the ECCD signal.

linker wraps over the nitrogen, it is believed that there will be steric interactions between the linker and the protecting group of the nitrogen. Finally to further reduce steric interactions, P2 will rotate away from the aziridine resulting in helical chirality of the porphyrins. For aziridine amides with an (*R,R*) configuration, the porphyrins are oriented in a clockwise fashion and a positive ECCD signal will be generated. The complex of C5-Zn-TPFP-Tz and (*S,S*) configured aziridine amides will result in a counterclockwise orientation of the porphyrins and a negative ECCD bisignate curve.

The sign of the ECCD signals for the (*R,R*)-*N*-MEDAM-*cis*-aziridine amides (Figure V.11 A) was surprising given that ECCD signals of opposite sign were observed for the configurationally

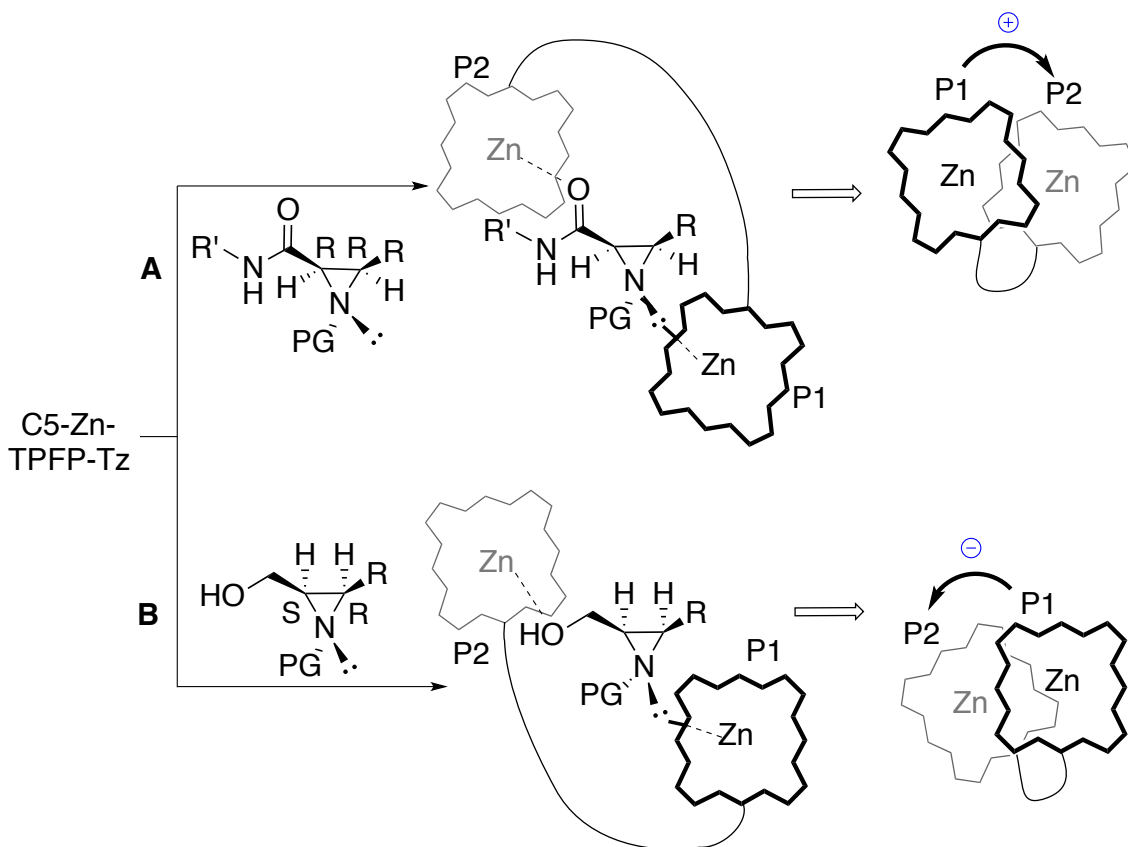


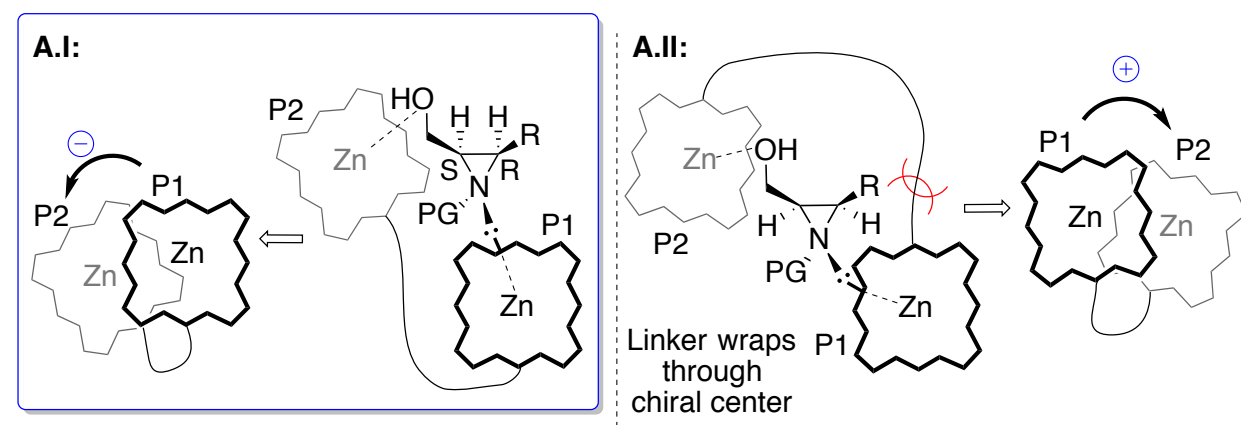
Figure V.11: Comparison of binding modes for *cis*-aziridines. **A:** *N*-protected-*cis*-aziridine amides and **B:** *N*-protected-*cis*-aziridine alcohols.

similar, (*S,R*)-*N*-protected-*cis*-aziridine alcohols (Figure V.11 B). Note that the apparent change in configuration at C2 is due to the change of the substituent which, according to the Cahn-Ingold-Prelog rules, causes a change in priority for the groups at that center. All of these substrates have a protected nitrogen as a binding functionality. But, they differ at the second binding site which is an alcohol for **V.4** and an amide for **V.6 -V.8**.

It is thought that the amide binding site has fewer degrees of rotational freedom as compared to the alcohol moiety. This restricted binding site must force the tweezer to bind in a different conformation than that for the aziridine alcohols leading to ECCD signals with the opposite sign. Figure V.12 summarizes the potential binding models of the *N*-protected aziridine alcohols and *N*-protected aziridine amides with the TFP-Tweezer. For the *N*-protected aziridine alcohols, there are thought to be two possible modes of binding. In both cases the porphyrin, P1, will bind to the nitrogen lone pair electrons from the opposite face as the protecting group and porphyrin, P2, binds with the hydroxyl from the opposite face of the aziridine as P1. The difference in binding models is that for **A.I** the linker wraps under the aziridine but for model **A.II** the linker wraps over the aziridine. The way the linker wraps around the aziridine will result in a sign switch of the ECCD signal. It is thought that **A.II** is disfavored as there is an increased interaction between the linker and the substituent of the C3 chiral center. Therefore, **A.I** is favored and a negative ECCD is expected for the (*S,R*)-*N*-protected-*cis*-aziridine alcohols.

A similar analysis of binding modes with the *N*-protected-*cis*-aziridine amides leads to four potential models. For all four cases the porphyrin, P1, will bind to the nitrogen lone pair electrons from the opposite face as the protecting group and porphyrin, P2, binds with the

A: Aziridine Alcohols



B: Aziridine Amides

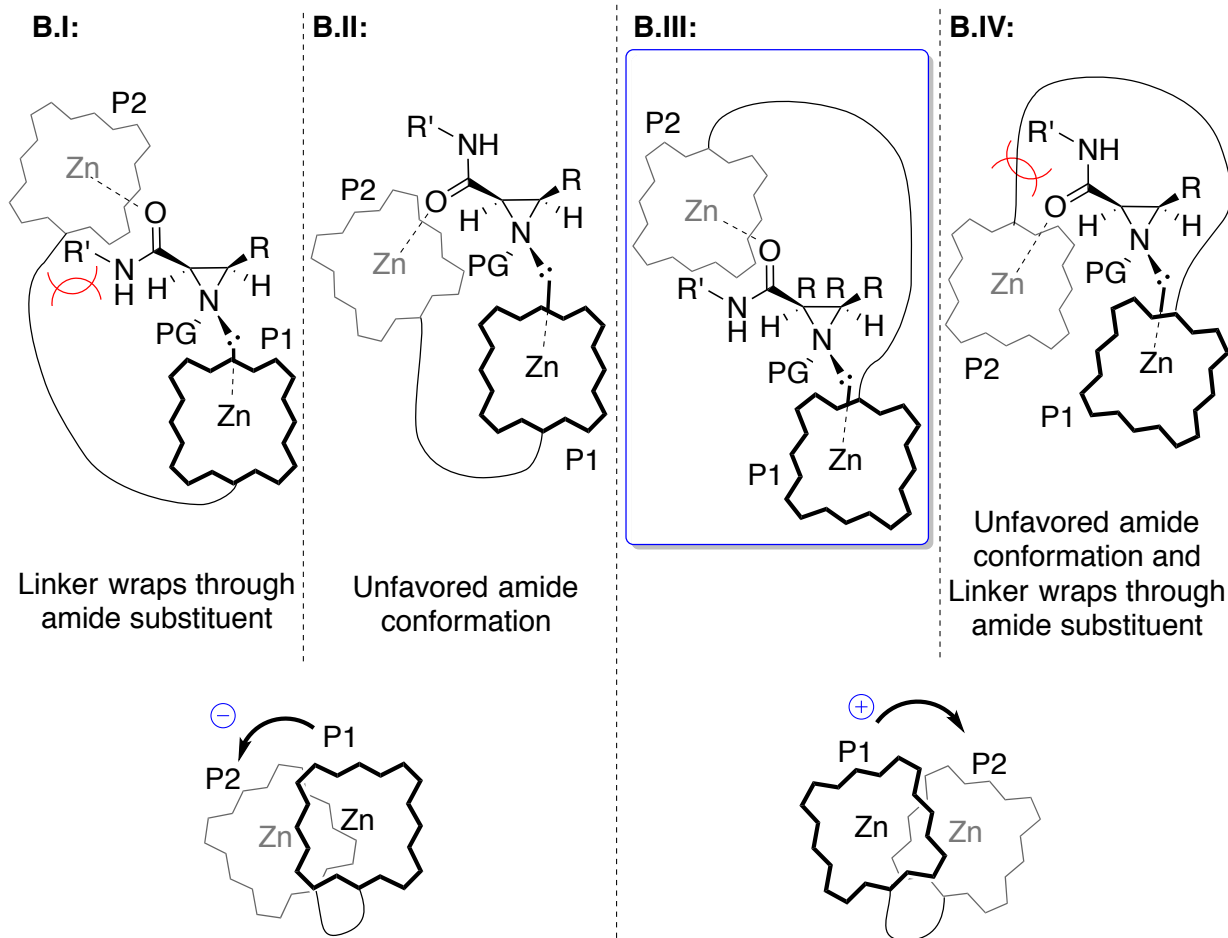


Figure V.12: Possible binding modes of the *N*-protected-*cis*-aziridines. **A:** Possible models for *N*-protected-*cis*-aziridine alcohols and **B:** *N*-protected-*cis*-aziridine amides.

See text for explanation.

amide from the opposite face of the aziridine as P1. In two cases, **B.I** and **B.II**, the linker of the tweezer wraps under the aziridine and for **B.III** and **B.IV**, the linker wraps over the top of the aziridine. There could also be conformational differences regarding the amide, specifically, the C-C bond between the carbonyl carbon and C2 of the aziridine. For models **B.I** and **B.III** the amide carbonyl is disposed *anti* to the aziridine C-N bond and for the other two models, **B.II** and **B.IV**, the amide carbonyl is *syn* to the aziridine C-N bond. The *syn* conformation of the amide carbonyl and the aziridine C-N bond is thought to be unfavored as this will result in the alignment of the dipole moments of these bonds. Therefore, models **B.II** and **B.IV** are also unfavored. The binding modes B.I and B.IV are thought to be unfavorable as the linker of the tweezer is brought in close proximity to the substituent of the nitrogen of the amide. The increased steric interaction would cause these binding models to be unfavored. Therefore, B.III is thought to be the favored binding model. The amide resides in the favored anti conformation and the linker will not have a steric interaction with the amide substituent. This binding model results predicts the positive ECCD signals that are observed for the (*R,R*)-*N*-MEDAM-*cis*-aziridine amides.

From these models, it can then be proposed that the conformation of the amide and the minimization of steric interactions with the amide substituent forces the tweezer to wrap around the (*R,R*)-*N*-MEDAM-*cis*-aziridine amides over C2 and C3 of the aziridine. This is the opposite way as the (*S,R*)-*N*-protected-*cis*-aziridine alcohols where the linker wraps under the nitrogen. As a result, the helicity of the porphyrins switches as does the predicted sign of the ECCD signal. Note: this analysis does not consider the effect of binding to the tweezer. It is possible that the preferred conformation of the aziridine within the binding pocket of the

tweezer is different than the what has been proposed. However, the proposed analysis does explain the signs of the ECCD signals that are observed.

V.3.2: ECCD Study of *trans*-Aziridine Amides

In addition to the *cis*-aziridine amides, a series of *N*-protected-*trans*-aziridine amides were also obtained from the Wulff lab. ECCD assignment of absolute configuration of the *trans* aziridine amides required development of a separate mnemonic as these are diastereomers of the *cis*-aziridine amides.

Figure V.13 summarizes the ECCD results for the *trans*-aziridine amides. This analysis was a combined effort with Dr. Li. Figure V.12 is separated into the substrates analyzed by Dr. Li (A) and those analyzed as a part of my studies (B). In total there were 19 *trans*-aziridine amides studied. Of these 19 substrates, four of the aziridines did not follow the general trend observed (**V.18**, **V.19**, **V.29** and **V.30**). For most substrates, ECCD signal was observed with as little as 0.2 equivalents of substrate and the tweezer was tolerant of both aryl and alkyl groups at the C3 carbon as well as the amide end of the substrates. In general, the (2*R*, 3*S*) configured aziridine amides generated negative ECCD and the (2*S*, 3*R*) aziridine amides provided positive ECCD.

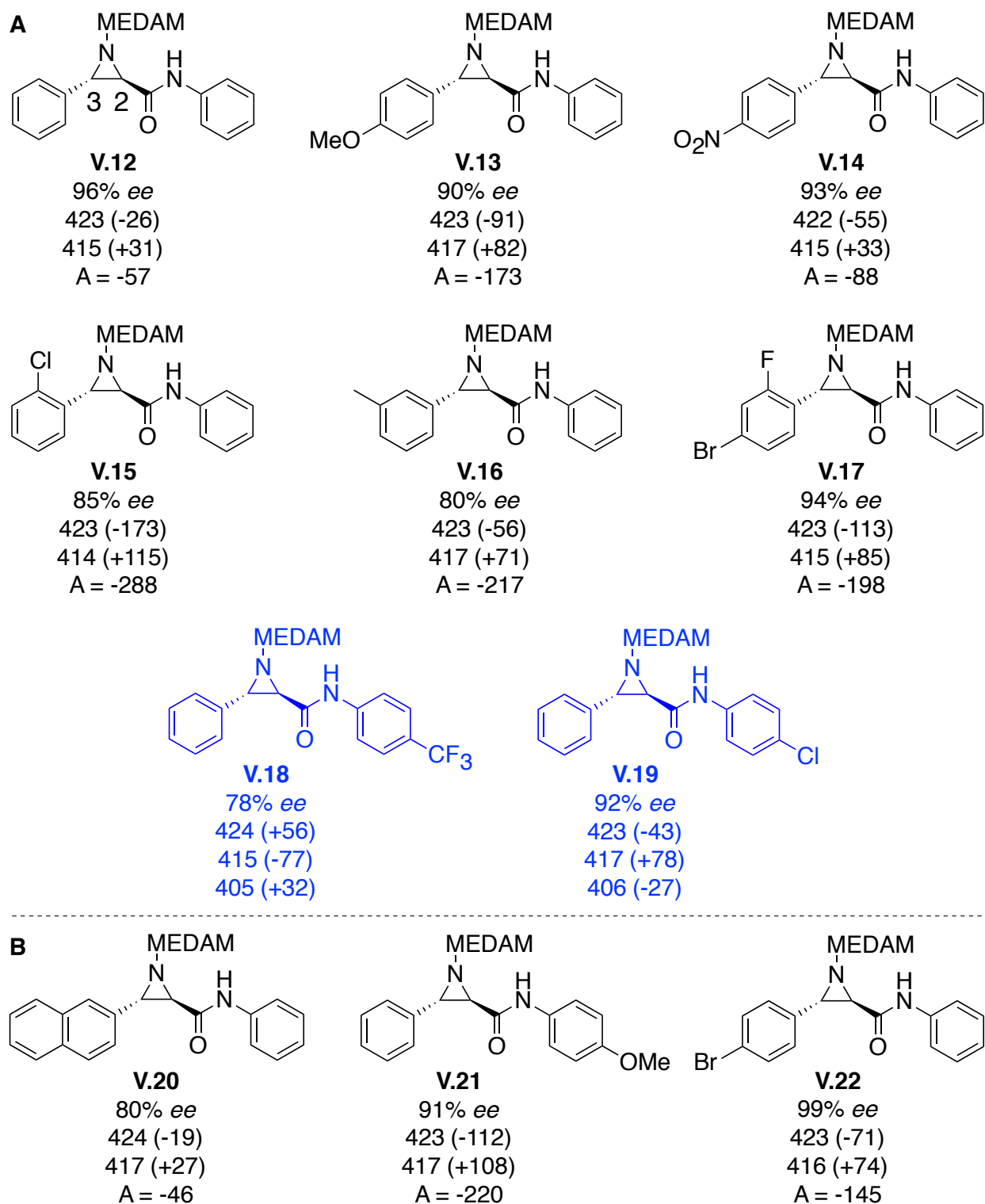
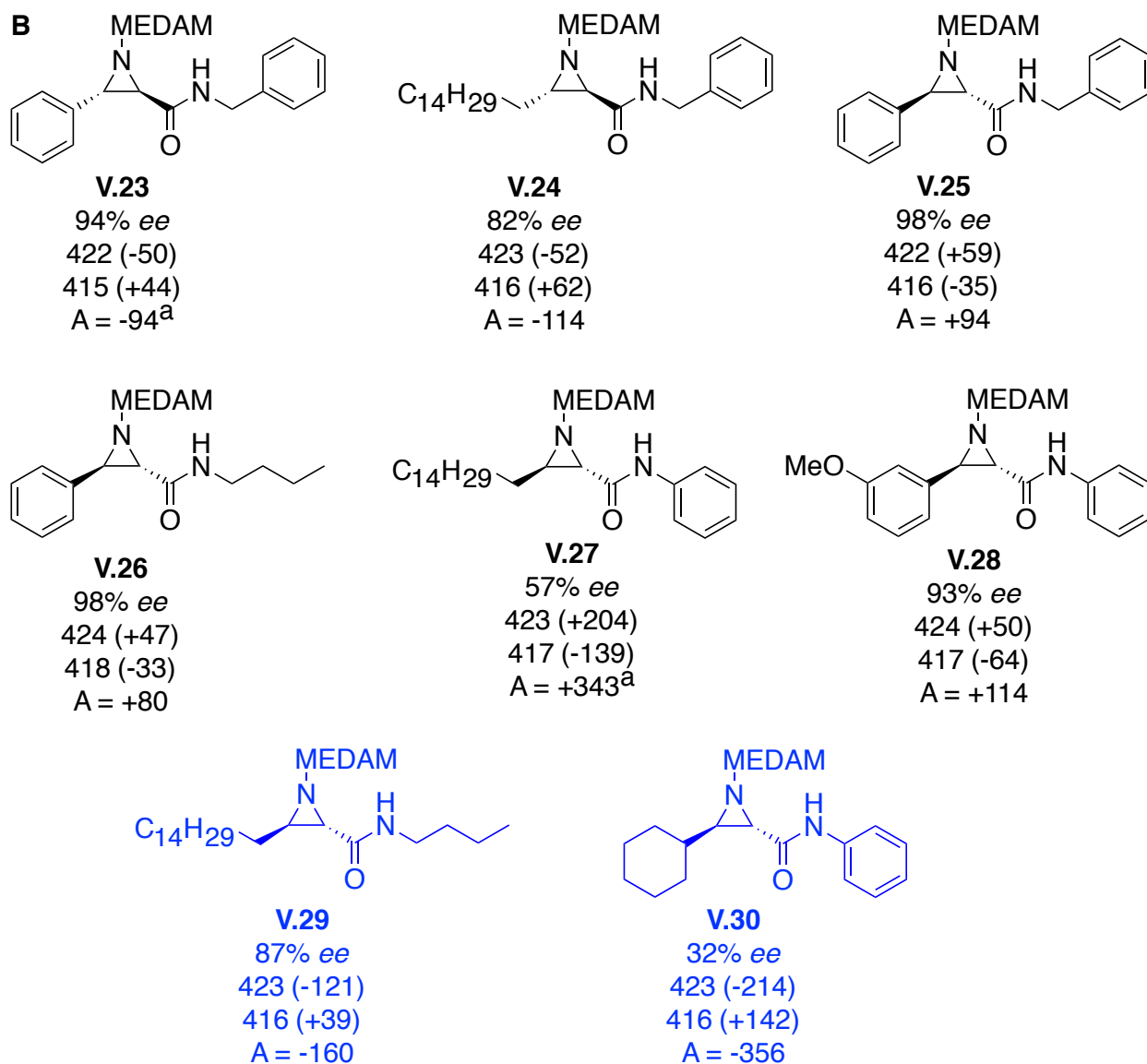


Figure V.13: ECCD analysis of *trans*-aziridine amides. Substrates in blue deviate from the general trend. All measurements: 2 μ M tweezer, hexanes, 0 $^{\circ}$ C, 5 equivalents of substrate. a: 20 equivalents of substrate. **A:** Analyzed by Dr. Li.

Figure V.13 (cont'd)



As before, UV-Vis analysis was also conducted for these substrates. For most substrates, there was approximately a 5 nm shift of the Soret band which indicates that a 1:1 tweezer-substrate complex had formed; Figure V.14 B provides the UV-Vis titration with **V.21**.

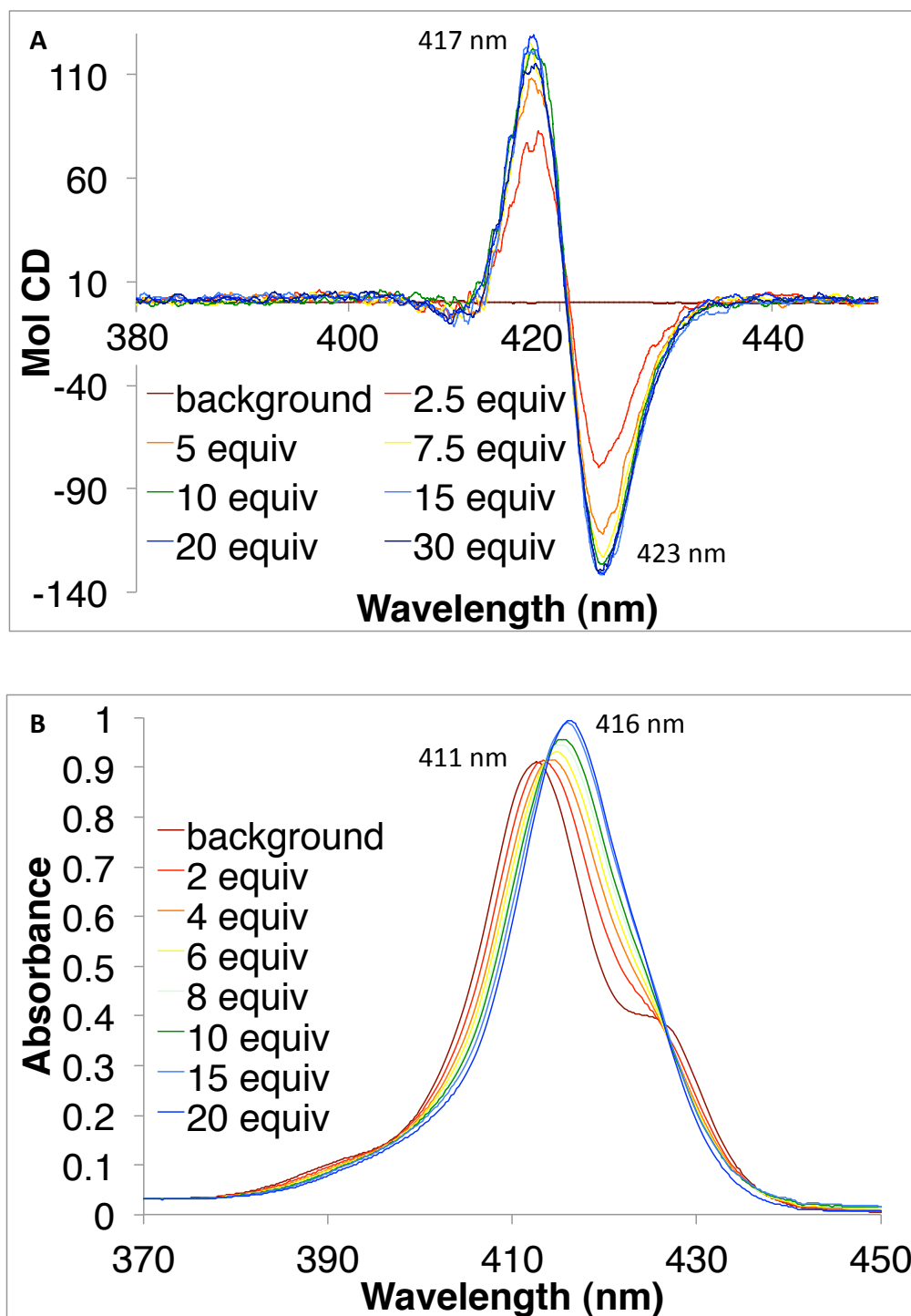
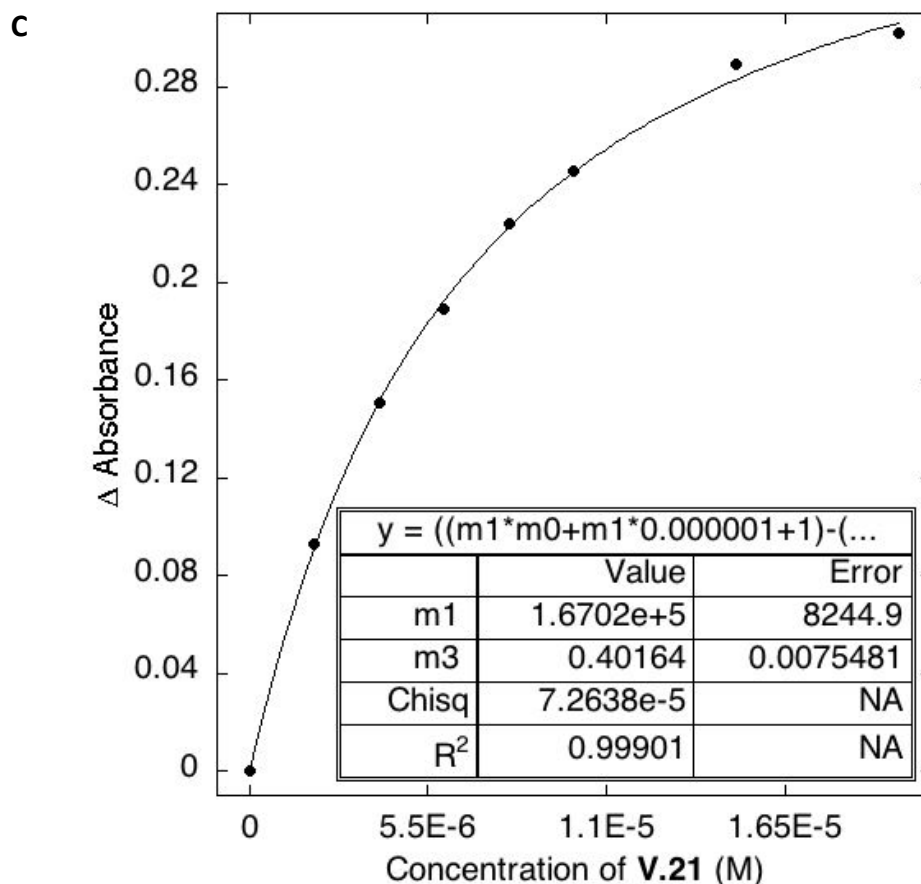


Figure V.14: Analysis of the C5-Zn-TPFP-Tz and **V.21** complex. **A:** ECD titration 2 μM Tz, hexanes, 0 $^{\circ}\text{C}$. **B:** UV-Vis titration 1 μM Tz, hexanes, room temperature.

Figure V.14 (cont'd): Analysis of the C5-Zn-TPFP-Tz and **V.21** complex. **C:** Binding constant calculation. 1 μ M Tz, hexanes, room temperature.



Binding constant determination for substrate **V.21** elucidated a binding constant of $1.6 \times 10^5 \text{ M}^{-1}$ which is of similar magnitude as the *cis*-aziridine amides. Being that all of the aziridine amides have similar binding functionalities, *N*-MEDAM protected nitrogen and an amide, it is not surprising that all of these substrates have similar binding affinities for the tweezer.

The binding model for these *trans*-aziridine amides is summarized in Figure V.15. As with the *cis*-aziridine amides, the location of the nitrogen protecting group is the largest factor governing the binding and transfer of chirality from the aziridine to the tweezer. It is assumed

functionality as the sp^2 carbon of the amide carbonyl at carbon 2 of the aziridine should be sterically smaller than the R group at carbon 3 of the aziridine. Furthermore, this conformation of the nitrogen will force the nitrogen lone pair electrons to the opposite face as the aziridine. This places the binding functionalities *anti* to one another which is preferred for formation of the host-guest complex as this will situate the porphyrins *anti* to one another. With the

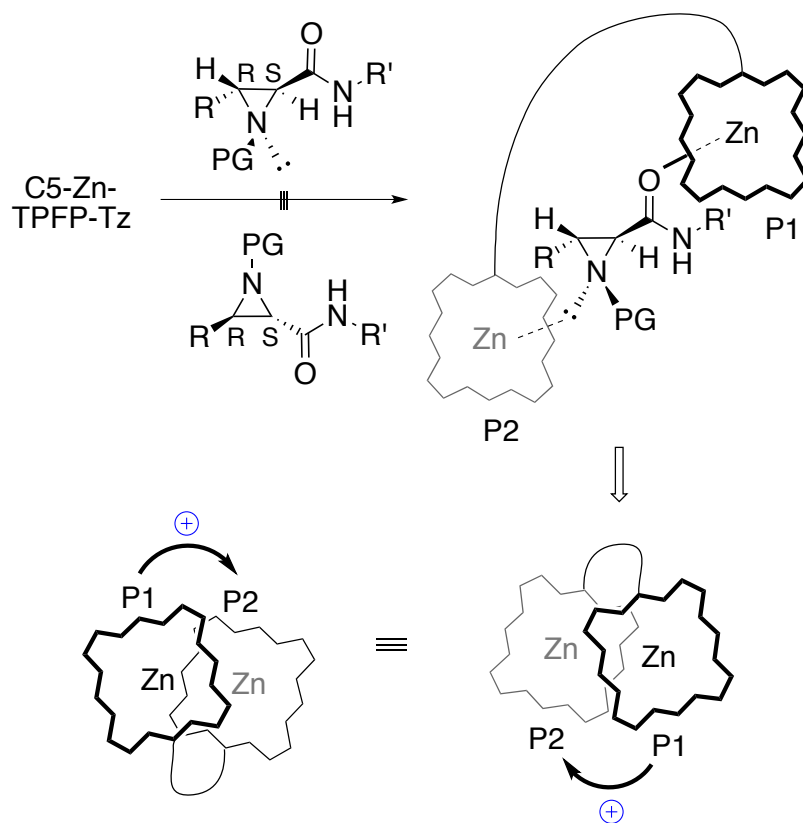


Figure V.15: ECCD model for *N*-protected-*trans*-aziridine amides. An (2*S*, 3*R*) configured aziridine amide is shown. Pyramidalization of the nitrogen favors placement of the protecting group to the opposite face of the aziridine substituents. Minimization of steric factors results in the helicity of the porphyrins and the expected sign of the ECCD signal.

assumption that this is the preferred conformation of the aziridine, binding of the porphyrins occurs in a manner to minimize steric interactions between the porphyrins and the aziridine. The porphyrin that binds with the amide carbonyl approaches from the same face of the aziridine as the protecting group and rotates away from the aziridine. The second porphyrin, P2, binds to the opposite face of the aziridine to minimize porphyrin-porphyrin interactions. This porphyrin will rotate toward P1 to minimize steric interaction with the aziridine substituent. Overall, this predicts a clockwise arrangement of porphyrins and a positive ECCD bisignate curve for (2*S*, 3*R*) configured aziridine amides. Additionally, this model predicts a counterclockwise arrangement of porphyrins for the (2*R*, 3*S*) configured aziridine amides and explains the negative ECCD signal.

Finally, five BUDAM protected *trans*-aziridine amides were also analyzed by ECCD and UV-Vis titration. The BUDAM protecting group is larger than the MEDAM protecting group therefore, it was anticipated that the protecting group of these substrates could inhibit binding and would test the limits of the C5-Zn-TPFP-Tz. All of these substrates provided weak and noisy ECCD signals and in one case, **V.31**, no signal was observed (Figure V.16). Large excess of the substrate was necessary to observe ECCD signal which is an indication the aziridines are weakly binding substrates. The binding constant for substrate **V.32** was calculated to be $\sim 10,000 \text{ M}^{-1}$ which is 10-fold smaller than the MEDAM protected aziridines. It is hypothesized that the weak binding of the substrate leads to the inconsistent ECCD results. The poor binding of the substrate could allow the complex to sample a number of ECCD active conformations which average together into the weak signals. Therefore, determination of absolute configuration for BUDAM protected aziridine amides cannot be achieved with C5-Zn-TPFP-Tz.

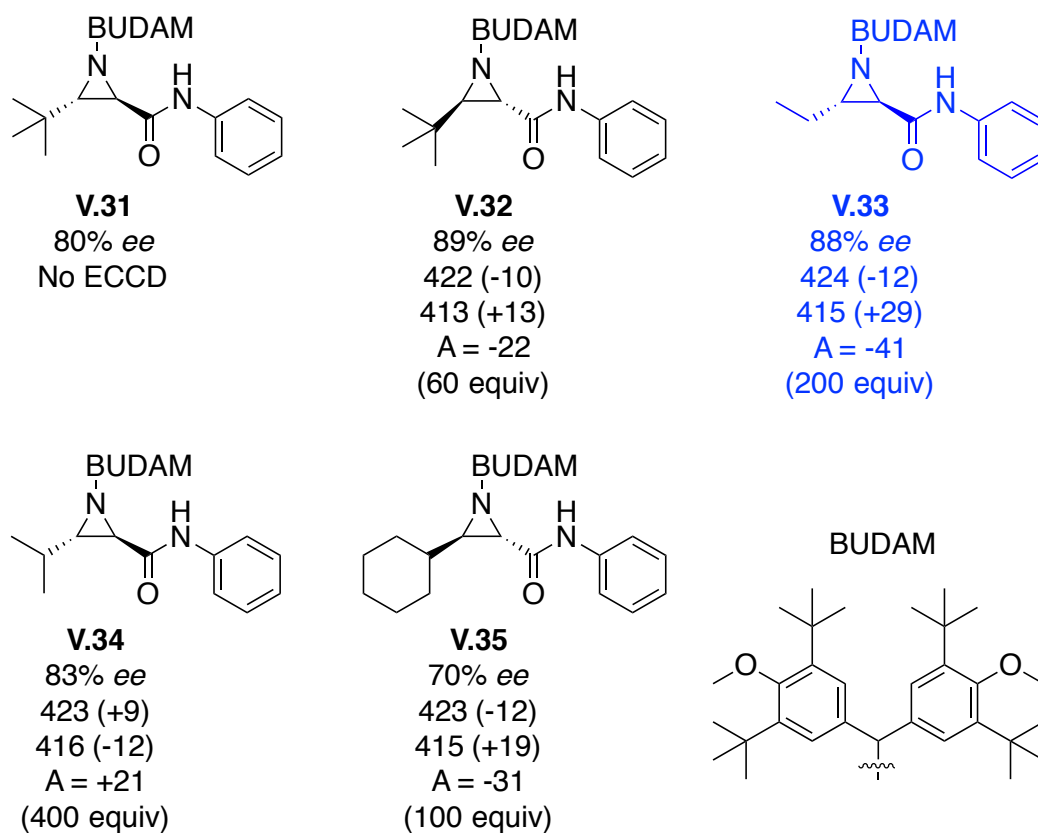


Figure V.16: Summary of the ECCD results for the BUDAM protected *trans*-aziridine amides. All measurements: 2 μ M tweezer, hexanes, 0 $^{\circ}$ C.

V.4: Conclusions on the Aziridine Amides

ECCD and UV-Vis analysis of six *cis*-aziridine amides and 19 *trans*-aziridine amides, obtained from the Wulff lab, allowed for the development of mnemonics for both classes of aziridines. These substrates exhibit similar binding affinities for the porphyrin tweezer (10^5 M^{-1}) and ECCD signals are observed with as little as 0.2 equivalents of the aziridine, at concentrations of 10^{-6} M. For both classes of substrates, the pyramidalization of the nitrogen dictates the location of the protecting group on the nitrogen of the aziridine. The preferred

pyramidalization is that which situates the protecting group of the nitrogen to the same face of the aziridine with the smallest substituents on the aziridine carbons. Once the preferred pyramidalization of the nitrogen is determined, binding of the tweezer, helicity of the porphyrins and the sign of the ECCD signal was predicted. This system is tolerant of aryl and alkyl substituents at C3 and the amide but is limited by the size of the nitrogen protecting group as demonstrated with the BUDAM protected aziridines. It is thought that this large protecting group inhibits substrate binding and leads to weak and inconsistent ECCD signals.

V.5: ECCD Study of *cis*-Epoxy Amides

Most recently, members of the Wulff lab demonstrated that *cis*-epoxy amides can be synthesized using a similar protocol for the synthesis of the *cis*-aziridine amides. In total, 17 *cis*-epoxy amides were generously donated for ECCD and UV-Vis analysis. As discussed above, an ECCD mnemonic was developed for the determination of absolute configuration of epoxy alcohols. This study proved that an epoxide oxygen is a suitable binding functionality for the electron deficient C5-Zn-TPFP-Tz.⁴² Additionally, from the ECCD studies of derivatized substrates, it was known that amide functionalities could also participate in a binding interaction with the porphyrin tweezers.^{44,45} Therefore, it was hypothesized that the epoxy amides would bind with C5-Zn-TPFP-Tz through binding interactions with the epoxide oxygen and the oxygen of the amide carbonyl.

Fortunately, all 17 substrates did produce an ECCD signal (Figure V.17). Initially, the substrates were analyzed with C5-Zn-TPFP-Tz at 0 °C in hexanes following the reported protocol for the epoxy alcohols.⁴² Under these conditions, there were several substrates that provided

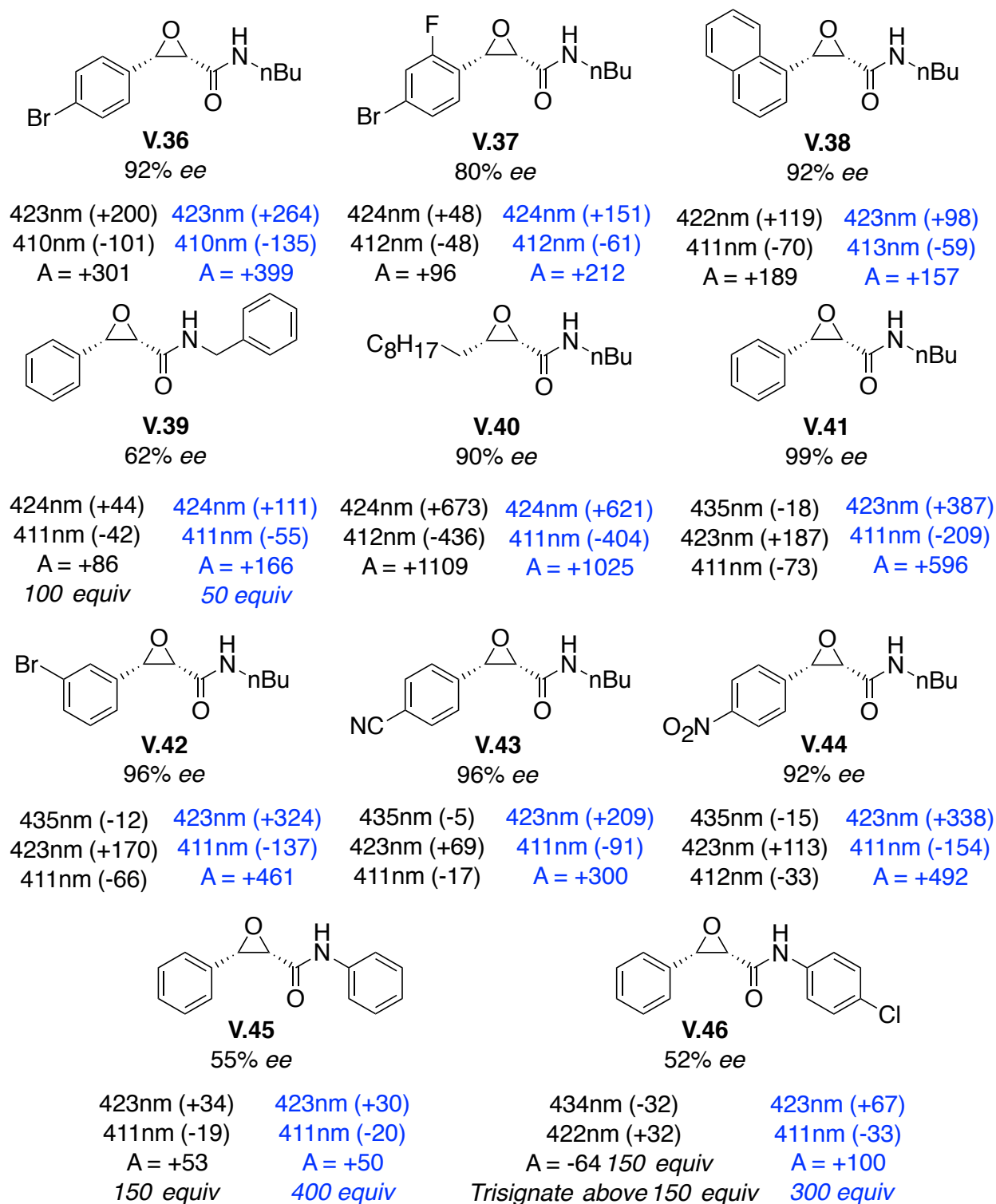
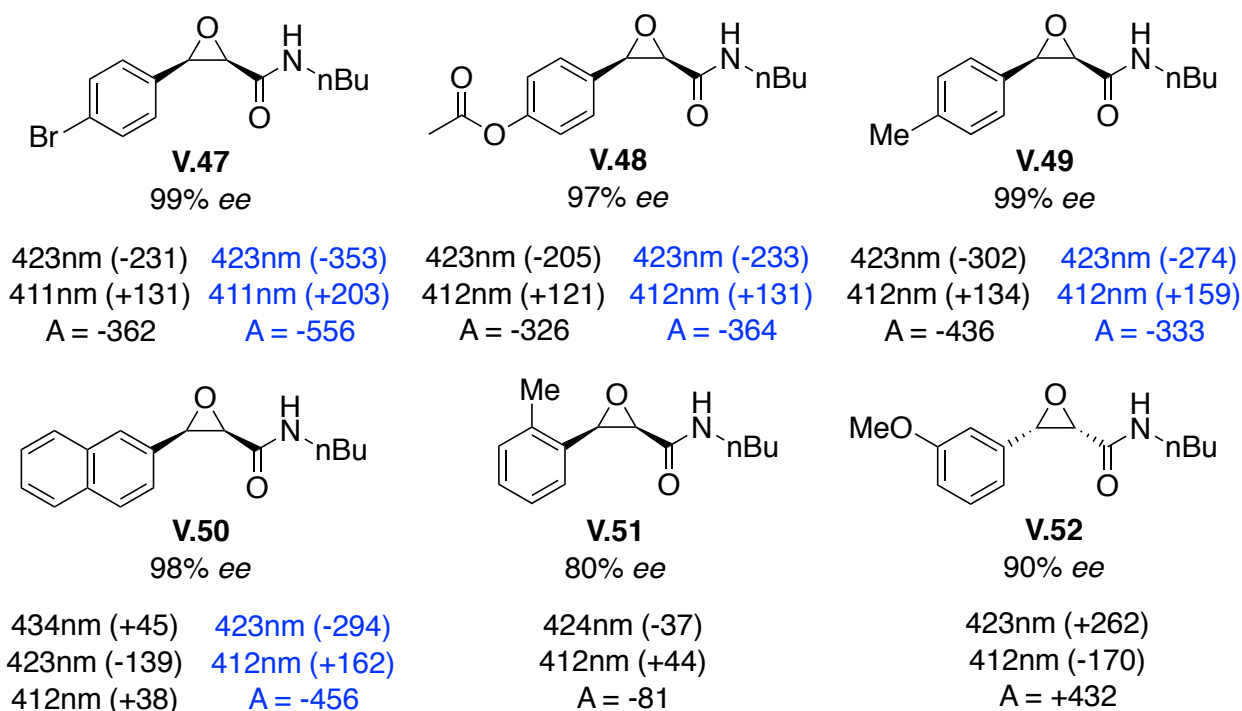


Figure V.17: Summary of the ECCD results for *cis*-epoxy amides. All measurements: 2 μ M tweezer, hexanes, 0 °C (black) or room temperature (blue), 40 equivalents of substrate unless otherwise noted.

Figure V.17 (cont'd)



trisignate, weak or noisy ECCD signals. Figure V.18 A provides an overlay of the ECCD conditions screened for substrate **V.44**. To improve the ECCD signals, a ECCD titration of Zn-C3-TPFP-Tz and Zn-C8-TPFP-Tz with **V.44** was conducted. These tweezers were optimal for other substrates and it was hypothesized that perhaps the C5-Zn-TPFP-Tz was not the ideal tweezer of the epoxy amides. Each of the three tweezers used provided complex ECCD signals with peaks at approximately 435 nm, 424 nm and 412 nm. These complex signals suggest that the host-guest complex is sampling a number of ECCD active complexes. Summation of the ECCD

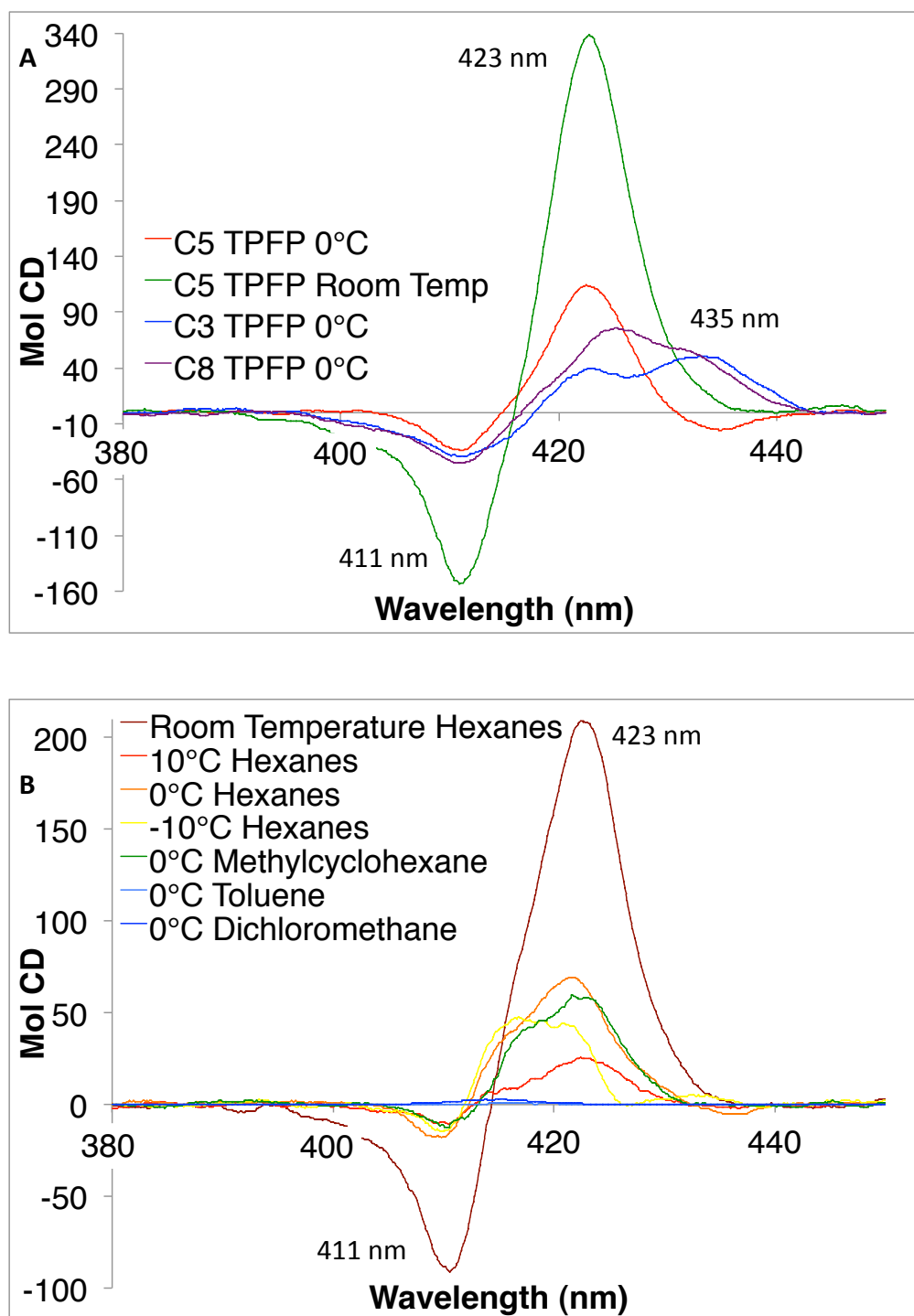


Figure V.18: Overlay of the ECCD conditions screened. **A:** For **V.44**, C5-Zn-TPFP-Tz at room temperature provided the most intense signal. **B:** Temperature and solvent screen with **V.43**. All measurements: 2 μ M tweezer, hexanes, 40 equivalents of substrate.

signals for all ECCD active complexes could result in the noisy, trisignate spectra.

Next, an ECCD titration of C5-Zn-TPFP-Tweezer with **V.44** at room temperature was conducted. Under these conditions, an intense bisignate ECCD response was detected. ECCD measurements of the remaining substrates at room temperature were taken (Figure V.17, highlighted in blue). Fortunately, the change in temperature led to a general protocol for ECCD analysis of epoxy amides. A more thorough temperature and solvent screen was conducted with **V.43**. Again, room temperature in hexanes were found to be the ideal conditions (Figure V.18 B) Typically, lowering the temperature reduces the number of ECCD active conformations that are accessible to the host-guest complex which enhances the ECCD signal that is observed. For the *cis*-epoxy amides, it is thought that the lower temperatures prevent the complex from accessing a favorable conformation. By raising the temperature, the complex can adopt a new conformation which is responsible for the stronger ECCD signals.

As expected, the enantiomeric pair of epoxy amides, **V.36** and **V.47**, provide ECCD signals of opposite sign (Figure V.19 A). Furthermore, all epoxy amides bearing an (*S,S*) configuration (**V.36** - **V.46**) generate a positive ECCD signal and all epoxy amides bearing an (*R,R*) configuration (**V.47** - **V.52**) provide negative ECCD signals with 40 equivalents of the substrate.

Again, UV-Vis titrations of C5-Zn-TPFP-Tz were also conducted. Upon binding of the epoxy amide, the Soret band of the porphyrin shows little shift, 1 nm or less. At high concentration of epoxy amide, greater than 100 equivalents in most cases, the Soret band shifts to 417 nm and the ECCD signal deteriorates which indicates that a 1:1 complex is transitioning to the ECCD inactive 2:1 complex. UV-Vis titration of C5-Zn-TPFP-Tz with **V.36** (Figure V.19 B)

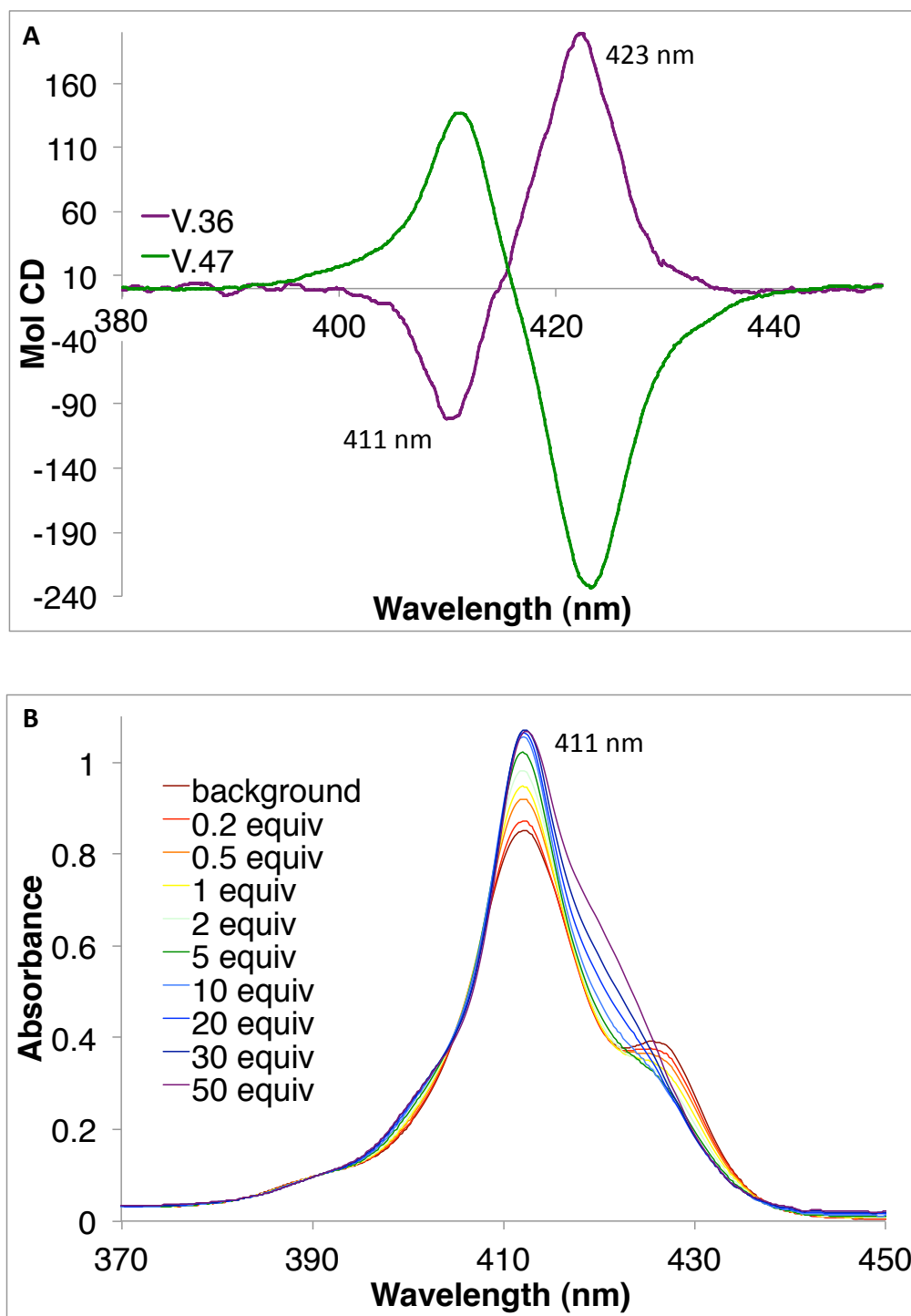
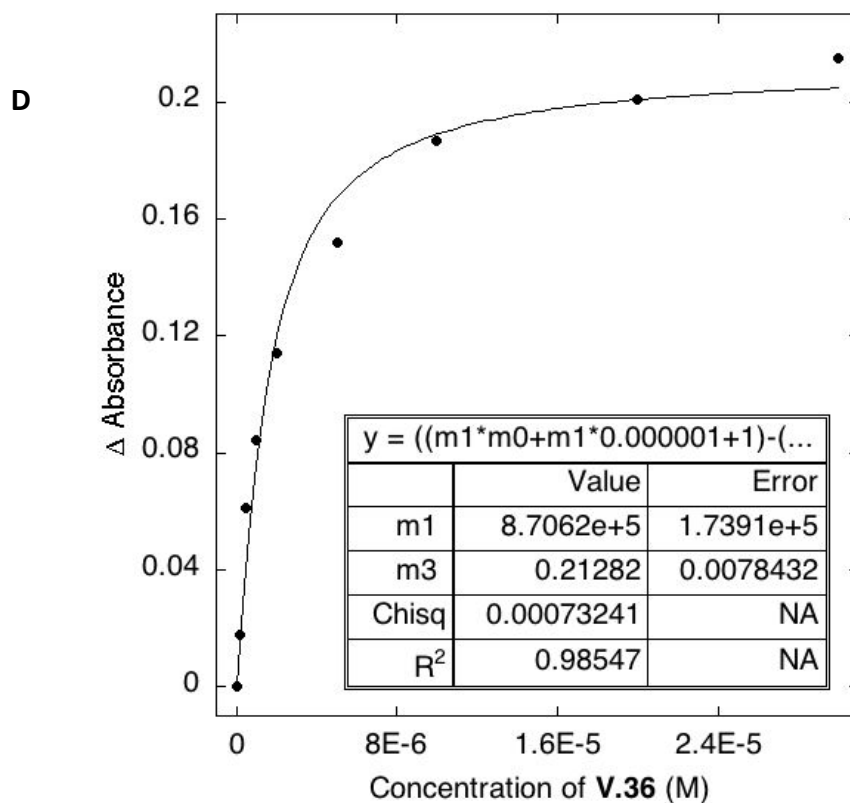
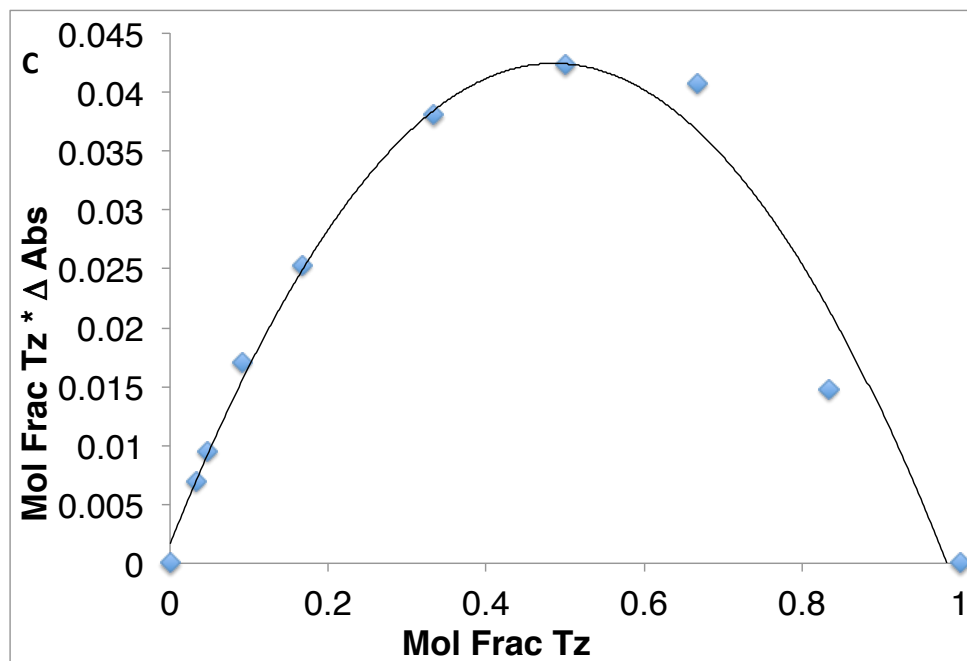


Figure V.19: Analysis of the C5-Zn-TPFP-Tz and **V.36** complex. **A:** ECD overlay of the enantiomeric pair **V.36** and **V.47**, 2 μ M Tz, hexanes, room temperature. **B:** UV-Vis titration 1 μ M Tz, hexanes, room temperature.

Figure V.19 (cont'd): Analysis of the C5-Zn-TPFP-Tz and **V.36** complex. **C:** Job's plot analysis and **D:** Binding constant calculation. 1 μ M Tz, hexanes, room temperature



was used for Job's plot analysis (Figure V.19 C) and determination of binding affinity (Figure V.19 D) for this class of substrates. A 1:1 complex is observed based on the Job's plot and a binding affinity of $8 \times 10^5 \text{ M}^{-1}$ was calculated. This binding constant is similar to the aziridine amides suggesting that the protected nitrogen of the aziridine binds approximately as strongly as the epoxide oxygen of the epoxy amides.

The proposed binding model for *cis*-epoxy amides is presented in Figure V.20. It is assumed that one porphyrin, P2, approaches the epoxide to coordinate with the oxygen lone

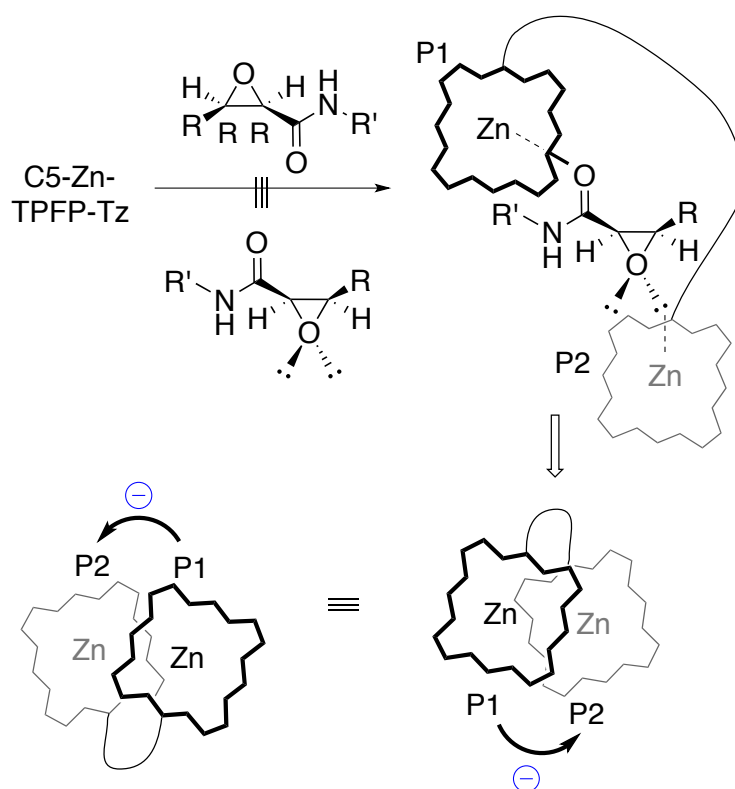


Figure V.20: ECCD model for *cis*-epoxy amides. (*R,R*) configured epoxy amide is shown.

Minimization of steric factors results in the helicity of the porphyrins and the expected sign of the ECCD signal.

pair electrons on the same face as the two hydrogen substituents. As the substituents on this face of the epoxide are the same size, no steric differentiation occurs and this porphyrin remains static. The other porphyrin will approach the epoxide, to bind with the amide, from the opposite face as P2 to avoid porphyrin-porphyrin interactions. Once bound, P1 rotates away from the R group at the adjacent carbon resulting in a helical conformation of the porphyrins. For (*R,R*) configured epoxides, the porphyrins should adopt a counterclockwise arrangement which explains the negative ECCD signal that is observed. A clockwise orientation of the porphyrins is predicted for the (*S,S*) configured epoxides and a positive ECCD signal is observed.

Interestingly, the configurationally similar epoxy alcohol **V.1** and epoxy amides **V.47 - V.51** generate ECCD signals of the opposite sign (Figure V.21). The same switch of sign for ECCD signals was observed for the *N*-protected aziridine alcohol **V.5** and the configurationally similar *N*-protected aziridine amides **V.6 - V.8**. Being that the switch of sign is a general trend observed for all substrates with an amide binding functionality, the amide must be causing the complex to favor a different binding mode. The same line of reasoning that was proposed for the *N*-protected *cis*-aziridines could be applied to the *cis*-epoxides. Similar to what was hypothesized above (Figure V.12), the porphyrin tweezer will wrap around the epoxy alcohol such that the steric interactions between the substituent at C3 of the epoxide and the linker of the tweezer are minimized. This results in the positive ECCD signals for the (*S,R*)-configured *cis*-epoxy alcohols. For the (*R,R*)-*cis*-epoxy amides, the preferred conformation amide functionality is such that the amide carbonyl is anti to the C-O bond of the epoxide. When bound, the porphyrin will wrap around the epoxy amide so to minimize interactions with the amide

substituent resulting in a counterclockwise helicity of the porphyrins and a negative ECCD bisignate curve. Again, it is minimization of interactions between the tweezer and the amide of the epoxide that causes the switch in sign of the ECCD signal for these configurationally similar substrates.

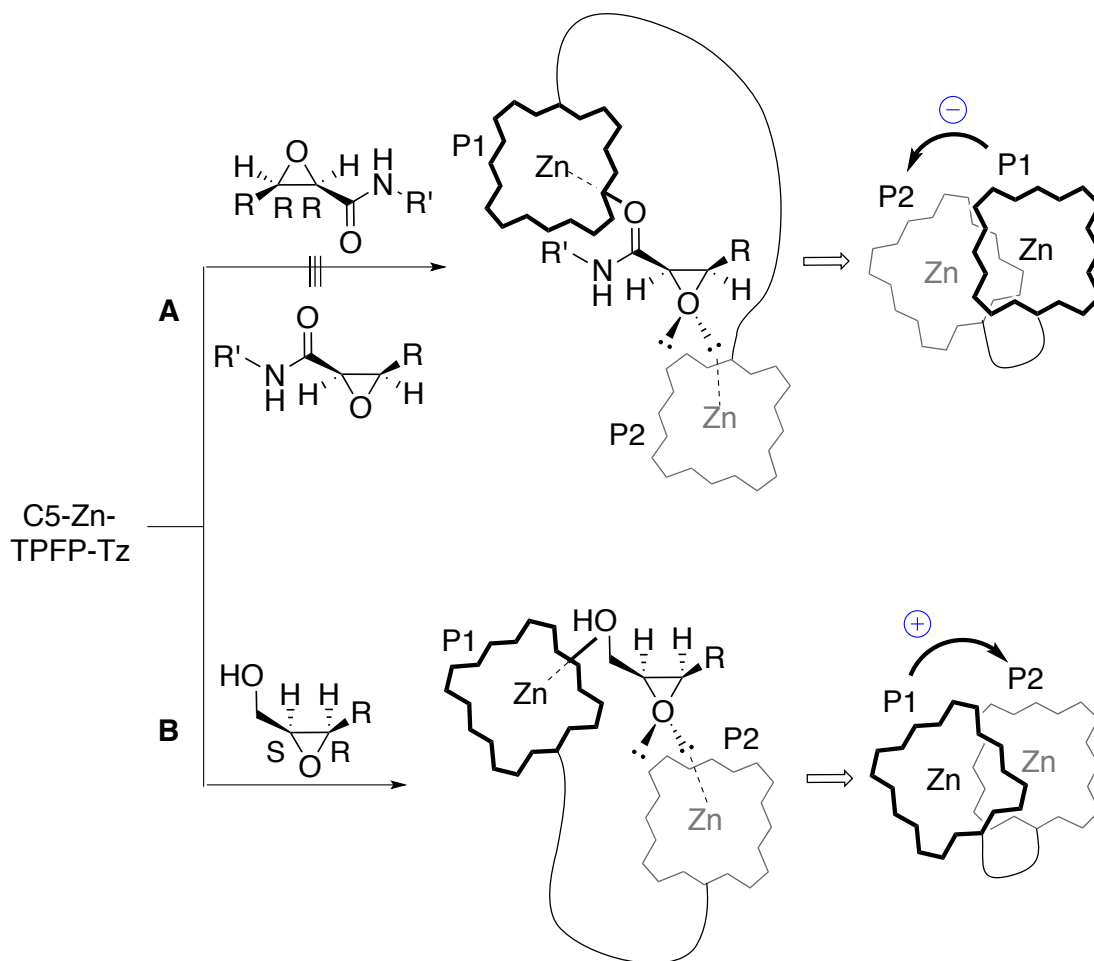


Figure V.21: Comparison of binding modes for *cis*-epoxides. **A:** *cis*-epoxy amides and **B:** *cis*-epoxy alcohols.

V.6: Conclusions on the Epoxy Amides

A total of 19 *cis*-epoxy amides were subjected to ECCD and UV-Vis analysis. ECCD with C5-Zn-TPFP-Tz at room temperature was found to be the optimum conditions for analysis. The

tweezer was found to be tolerant of alkyl and aryl substituents at both C3 of the epoxide and as the substituent of the amides. All of the substrates followed a general trend based on the configuration of the epoxide carbons. A mnemonic was developed to explain the observation of a negative ECCD bisignate curve for all (*R,R*) substrates and a positive ECCD signal for the (*S,S*) epoxy amides. UV-Vis showed little shift of the porphyrin Soret band when the ECCD active complex. Job's plot analysis showed that a 1:1 complex was formed and the binding affinity was calculated to be $8 \times 10^5 \text{ M}^{-1}$. Finally an overarching trend for all amide substrates (aziridine and epoxide) was found. These substrates provide ECCD signals of opposite sign as the configurationally similar aziridine or epoxy alcohols. This observation suggests that the amide changes the binding mode, orientation of the porphyrins and sign of the ECCD signal.

V.7: Experimental Procedures

V.7.1: General Procedure for ECCD Measurement

To hexanes (1 mL) in a 1.0 cm cell, 2 μL of a 1 mM stock solution of zinc porphyrin tweezer (C5-Zn-TPFP-Tz) in anhydrous CH_2Cl_2 was added to provide a 2 μM tweezer solution. The background spectrum was recorded from 380 nm to 450 nm at a scan rate of 50 nm/min at the specified temperature. Each chiral guest molecule was dissolved in anhydrous CH_2Cl_2 to afford a 1 mM solution then 0.2 to 100 μL of this solution was added to the cell with the tweezer solution affording the host-guest complex. For substrates that required high concentration of guest, a 10 mM solution in anhydrous CH_2Cl_2 was prepared then 1 to 100 μL of this solution was added to the cell with the tweezer solution. The ECCD spectra was immediately recorded following addition of the guest solution (minimum of 4 accumulations). The resultant ECCD spectra, which is reported in millidegrees, was normalized to the tweezer concentration to obtain molecular CD (Mol CD).

V.7.2: General Procedure for UV-Vis Measurement, Job's Plot Analysis, and Binding Constant Determination

To hexanes (1 mL) in a 1.0 cm cell, 1 μL of a 1 mM stock solution of zinc porphyrin tweezer (C5-Zn-TPFP-Tz) in anhydrous CH_2Cl_2 was added to provide a 1 μM tweezer solution. The background spectrum was recorded from 600 nm to 350 nm at a scan rate of 240 nm/min at room temperature. Each chiral guest molecule was dissolved in anhydrous CH_2Cl_2 to afford a 1 mM solution then 0.2 to 100 μL of this solution was added to the cell with the tweezer solution affording the host-guest complex. For substrates that required high concentration of

guest, a 10 mM solution in anhydrous CH₂Cl₂ was prepared then 1 to 100 µL of this solution was added to the cell with the tweezer solution. The UV-Vis spectrum was collected immediately after addition of the guest solution.

The UV-Vis measurements were manipulated for the purpose of determining the complex stoichiometry by Job's plot analysis. First, the molar fraction of tweezer in the solution was first determined by dividing the moles of tweezer by the total number of moles (moles of tweezer and moles of guest molecule) present in solution. Second, the change in absorbance with each addition of guest molecule was determined. The molar fraction of tweezer and the change of absorbance were multiplied together. The Job's plot was generated by plotting molar fraction tweezer versus molar fraction tweezer multiplied by change in absorbance in Excel. A parabolic curve is generated and the apex of the parabola provides the molar fraction of tweezer in the host-guest complex. A 1:1 complex is formed when the apex falls at a molar fraction of 0.5.

The UV-Vis measurements were manipulated for the purpose of determining the the binding affinity of the guest molecule for the tweezer. The concentration of the guest molecule was determined based on the equivalents of the guest added to the tweezer solution. Also, the change of absorbance for each addition of the guest was determined. Using, KaleidaGraph a plot of the concentration of guest versus the change in absorbance was generated and a line of best fit was calculated based on the following equation:

$$F = F_0 - \frac{1 + (P_T + R_T)K_a - \sqrt{(P_T - R_T)^2 K_a^2 + 2(P_T + R_T)K_a + 1}}{2(P_T K_a)} (F_0 - F_\infty)$$

F = absorbance of the tweezer at a given concentration of guest.

F_0 = absorbance of the tweezer without guest.

F_∞ = absorbance of the tweezer at saturation with the guest.

P_T = concentration of the tweezer.

R_T = concentration of the guest molecule.

K_a = binding constant.

All Aziridine and Epoxy Amides were generously provided by Dr. Wulff.

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Chapter VI

Development of a Tripodal Host Molecule for ECCD of Chiral Monoamines and Monoalcohols

VI.1: Background

VI.1.1: Conventional Methods of Determining Absolute Configuration of Chiral Alcohols and Amines

Chiral alcohols and amines are common and important classes of molecules through out chemistry. These functionalities are often observed in natural products, chiral building blocks and ligands for asymmetric catalysis. Even with the ever increasing number of methodologies allowing to access chiral alcohols and amines, there are still limited means by which the absolute configuration of these functionalities can be determined. The absolute configuration of alcohols and amines is most commonly determined by NMR methodologies. Mosher ester analysis, developed in 1969, was first conducted with chiral alcohols and amines.¹ The methodology has since been extended to include other monofunctionalized molecules such as carboxylic acids.² This methodology has been described in detail in Chapter 1. For crystalline samples, X-ray crystallography has been utilized for determination of configuration. Another common option is to derivatize the alcohol or amine into a molecule of known configuration, then by comparison of optical rotations, the configuration can be established.

There are few CD based methodologies for monoalcohols and monoamines. To date, the vast majority of CD methodologies are limited by the requirement that the chiral guest molecule must contain two functionalities capable of coordination with the host molecule.

There are however, limited examples of systems designed to report the chirality of monoalcohols and monoamines are known.³⁻⁵

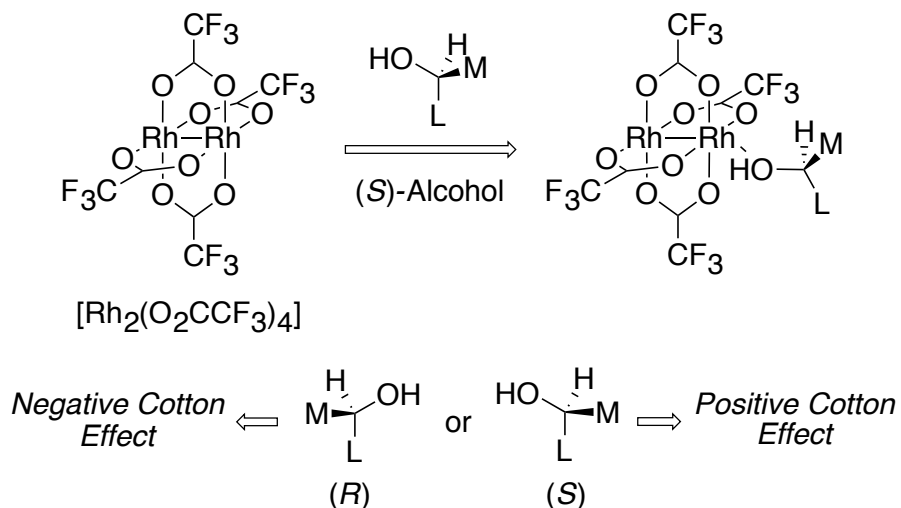


Figure VI.1: Gerards and Snatzke's methodology for determination of configuration of chiral alcohols using a rhodium (II) dimer.³

In 1990, Gerards and Snatzke reported a ruthenium based complex for determination of configuration for alcohols, ethers (including epoxides), ketones and olefins by CD (Figure VI.1).³ Cotton effects correlating to the configuration of the substrate were observed upon addition of the chiral substrate to a solution of rhodium(II)trifluoromethylacetate dimer ($[\text{Rh}_2(\text{O}_2\text{CCF}_3)_4]$). A sample of 10 chiral alcohols were evaluated and a general mnemonic was proposed based on the sign of the Cotton effect observed at the "E band" (~350 nm) for the complex. Alcohols of *R* configuration would provide a negative Cotton effect and alcohols of *S* configuration generated a positive Cotton effect. It is believed that the alcohol coordinates to the axial position of the rhodium complex. The induced asymmetry of the metal complex results from reducing steric

interactions with the substituents of the chiral alcohol. The overall chirality of the complex is observed.

Canary and coworkers have presented a method by which a primary amine was derivatized with two quinoline chromophores followed by complexation with copper (II) creates

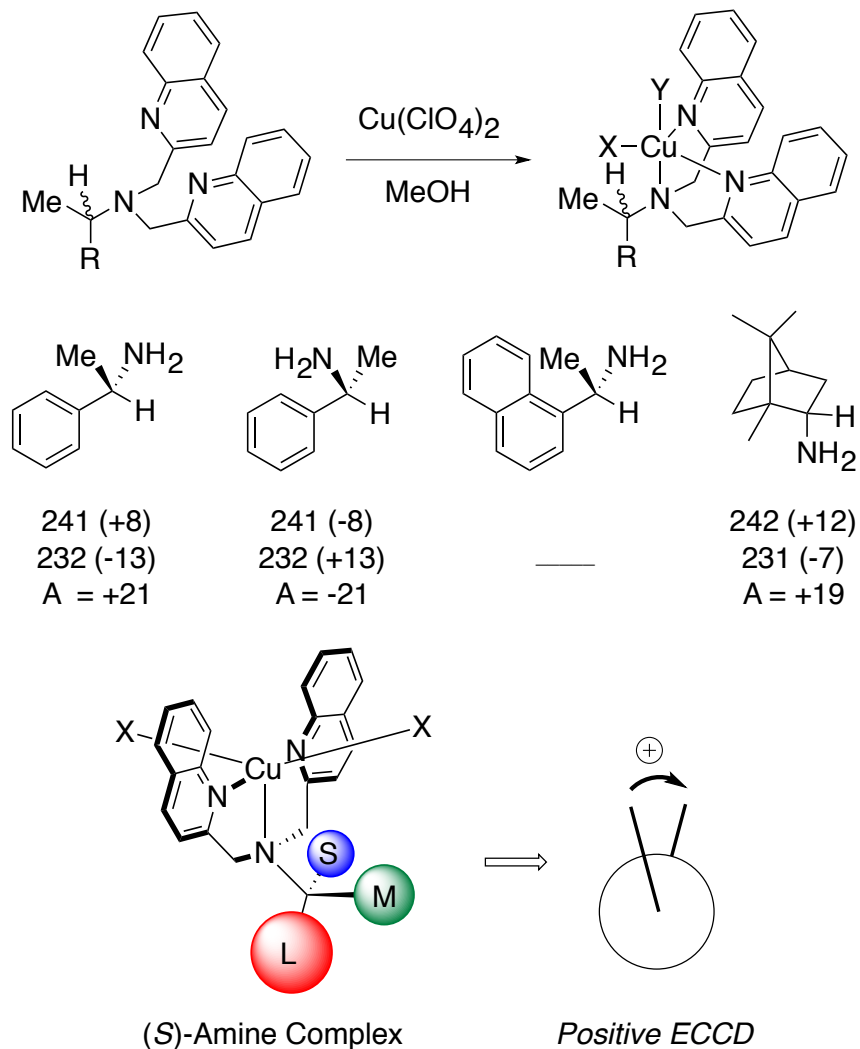


Figure VI.2: Derivatization of monoamines with quinoline chromophores followed by complexation with copper (II) perchlorate creates an ECD active complex. Sign of the signal is dictated by the configuration of the amine i.e. the location of the medium sized group.⁴

the chiral complex (Figure VI.2).⁴ The size amine substituents dictate the mode of binding and the rotation of the chromophores relative to one another. The substrate binds such that the large group resides in the least sterically congested sight, anti to the copper. The medium group interacts with and drives the nearest quinoline away while the quinoline nearest to the small group essentially remains static. In this manner, helicity between the chromophores is induced and an ECCD signal is observed. A mnemonic was developed. For (*S*) configured amines, a positive ECCD is expected. A notable pitfall of this methodology is the necessity to derivatize the amine prior to ECCD analysis.

Another system applied in the evaluation of monoamines is a zinc porphyrin system, developed by Inoue and co-workers (Figure VI.3).⁵ This host molecule is comprised of two zincated octaethylporphyrins attached by an ethylene linker. The chiral substrate binds axially with the metal of the porphyrin however, the short linker prevents the host from behaving as the zinc porphyrin tweezers. Therefore, this system does not require a guest with two sites of attachment. The rotation of the porphyrins relative to one another is dictated by steric interaction between the large group of the monoamine and the ethyl groups on the porphyrin. Amines bearing an (*R*) configuration consistently generated a negative ECCD signal while (*S*) amines would provide a positive couplet. This host system was extended to amino acids⁶ and then monoalcohols by changing the porphyrin zinc centers to magnesium, which is known to have stronger binding interactions with alcohols than zinc.⁷ There are limitations to this system. With smaller substituents, the ECCD amplitudes dwindle.⁸ Also, solvent⁹ and temperature¹⁰ can influence not only the intensity but the sign of the ECCD couplet.

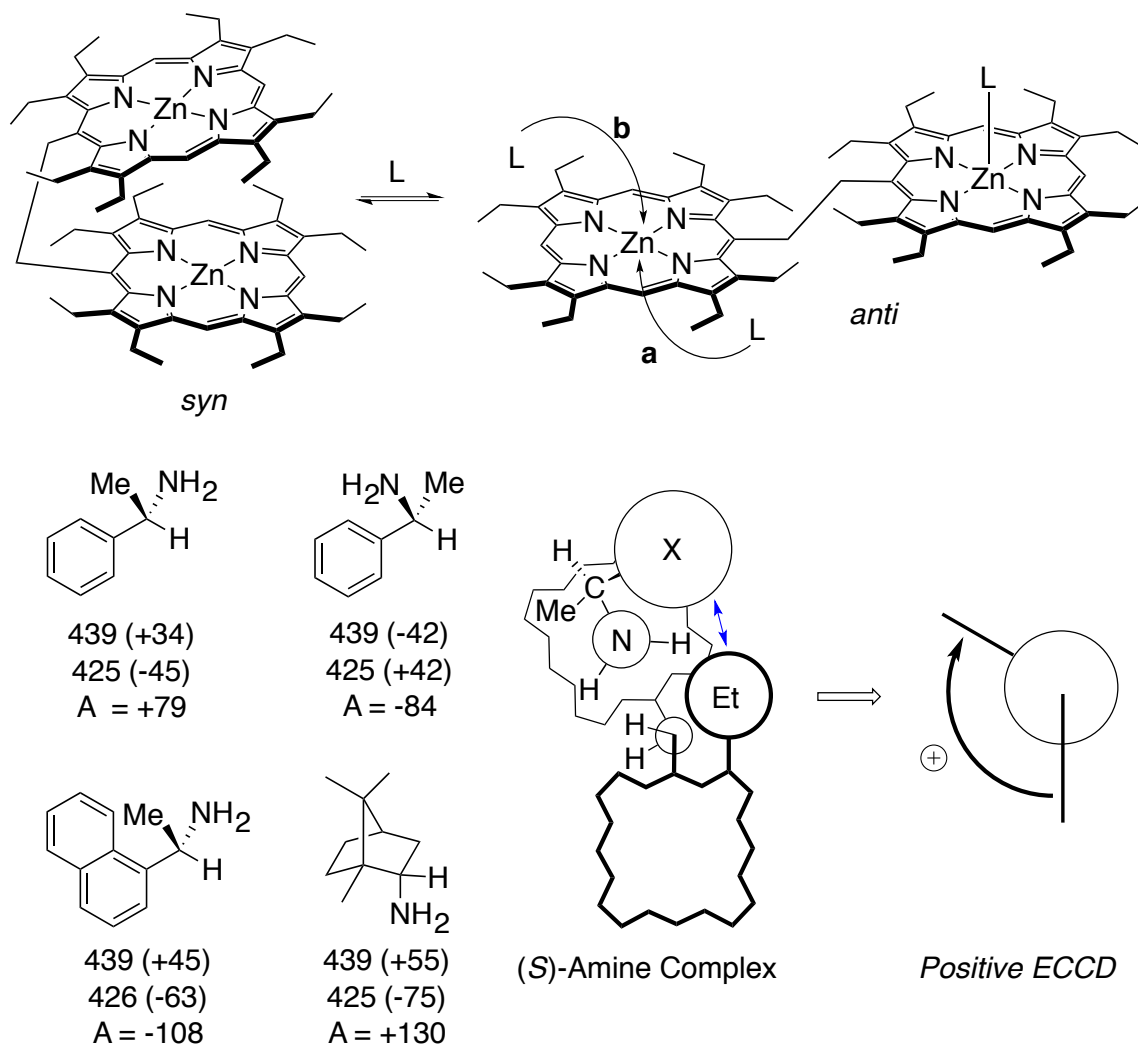


Figure VI.3: Two zinc porphyrins linked by an ethyl unit create an ECCD host for monoamines. Sign of the bisignate curve is dictated by the steric interaction between the large group on the amine and the ethyl group on the porphyrin.⁵

Finally, an ECCD protocol with Zn-TPP-Tweezer for the determination of configuration for alcohols and amines was reported by Nakanishi and coworkers (Figure VI.4).¹¹⁻¹³ The alcohol or amine substrate was first derivatized with 1,3-diaminopropane as a carrier to install the requisite two sites of attachment. Upon addition of the substrate to a solution of the tweezer a sandwich complex is formed. Once the substrate binds, the large group of the chiral

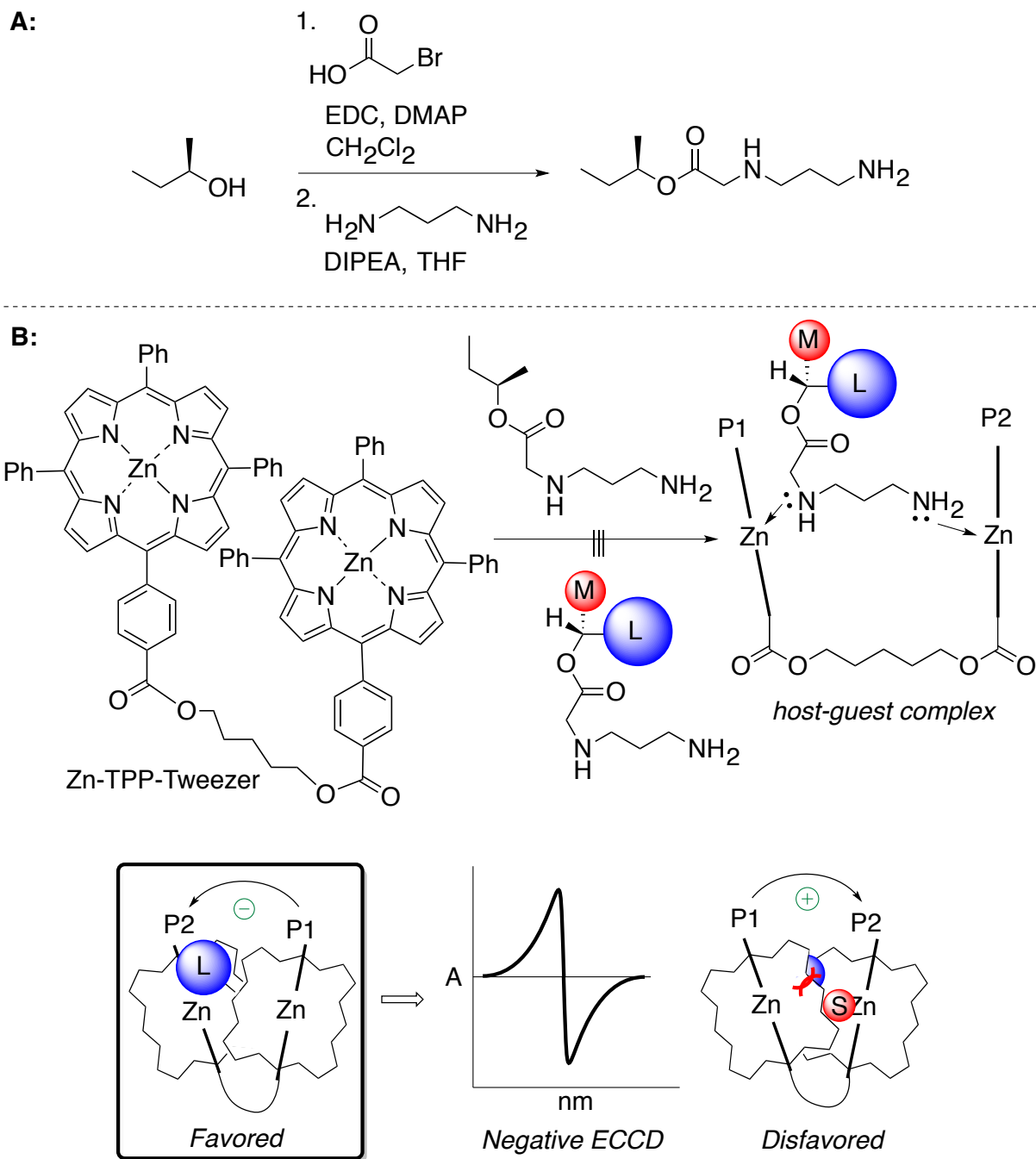


Figure VI.4: Porphyrin tweezer based ECCD protocol for determination of configuration of chiral amines and alcohols. **A:** Derivatization of (*R*)-2-butanol with the 1,3-diaminopropane carrier. **B:** Complexation of (*R*)-2-butanol with Zn-TPP-Tweezer. The sterics of this configuration of the alcohol predict a negative ECCD couplet.¹²

center rotates away from the porphyrin into the least sterically congested position. In this conformation, the small and medium groups face the porphyrin and to reduce steric interactions, the porphyrin slides toward the small group, thus leading to a helical twist of the tweezer complex. For alcohols and amines with an (*R*) configuration a negative ECCD is observed. A limitation to this method is the necessity for derivatization prior to complexation with the tweezer.

Although there are reliable methodologies available for determination of configuration of amine and alcohols most of them suffer the same limitation, namely the need for derivatization prior to analysis. This can, at times, limit the utility of the methodology particularly when the alcohol or amine is scarcely available. Thus, a general, reliable and non-empirical method for determination of absolute stereochemistry for alcohols and amines is still highly coveted.

VI.1.2: Tripodal Sensors for Ammonium Ions

Efforts to develop an ECCD active host system for chiral guest molecules with a single site of attachment, without chemical derivatization of the guest molecule, were inspired by the imidazole¹⁴ and oxazole^{15,16} based tripodal receptors designed for the selective recognition of ammonium cations. The first of these host systems was reported in 1999, by the Kim group. The authors disclosed the synthesis of an ammonium receptor that exhibited higher affinity for ammonium over potassium ions than nonactin.¹⁴ Commercially available ion-selective electrodes for ammonium contained nonactin however, the binding affinity of ammonium ions to nonactin is only ten fold larger than the binding affinity of nonactin for potassium cations.

Potassium and ammonium cations are similar in size therefore, it is difficult to achieve selectivity with a receptor that is selective based on cation size. However, the authors hypothesized that a selective ammonium receptor could be designed by incorporation of hydrogen bonding sites for additional interaction with the ammonium ion. At the core of this tripod was a hexasubstituted benzene elaborated with alternating ethyl and pyrazole arms. They found that the binding affinity for $\text{NH}_4^+ \cdot \text{PF}_6^-$ ($1.6 \times 10^6 \text{ M}^{-1}$) was two fold larger than the binding affinity for potassium ions ($8.8 \times 10^3 \text{ M}^{-1}$).

Soon after disclosure of the pyrazole tripod, the same group reported a structurally similar, oxazoline ligand that exhibited even greater selectivity toward ammonium ions.¹⁵ The oxazoline tripod shown in Figure VI.5 had a binding affinity of $2.5 \times 10^7 \text{ M}^{-1}$ for $\text{NH}_4^+ \cdot \text{PF}_6^-$ which

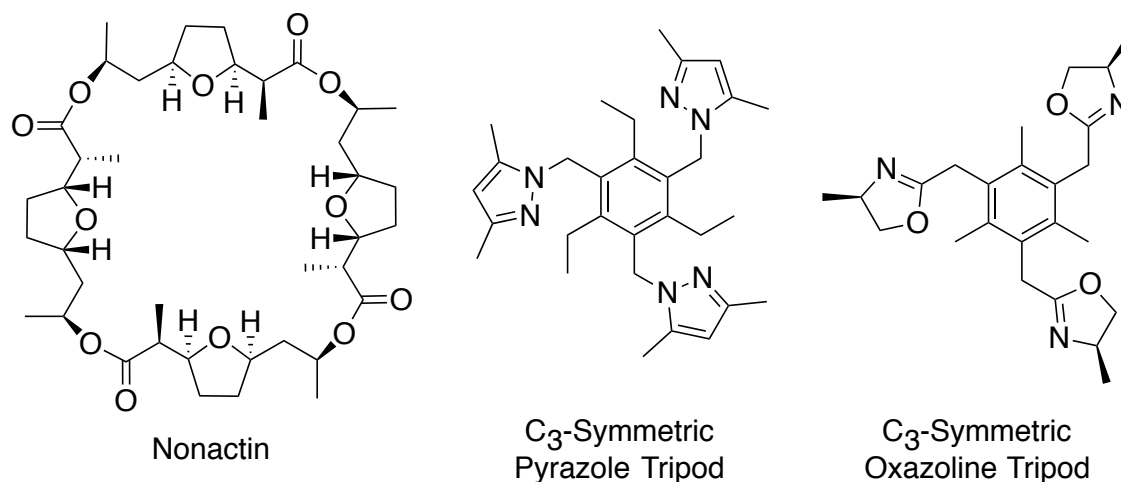


Figure VI.5: Structures of ammonium receptors. Nonactin is used in ion-selective electrodes shows limited selectivity for ammonium ions. The pyrazole tripodal system was designed to improve selectivity for ammonium ions or potassium cations.¹⁴ The oxazoline tripod soon followed the pyrazole tripod and exhibited even greater selectivity for ammonium cations.¹⁵

makes the tripod 400 times more selective for ammonium over potassium. This enhancement of selectivity was rationalized as a result of the increased basicity of the oxazoline ($pK_a = 5.0$) over the pyrazole ($pK_a = 2.5$) which in turn lead to stronger hydrogen bonding interactions with the ammonium.¹⁷ Calculations indicate that a complex of the oxazoline tripod with $NH_4^+ \cdot PF_6^-$ is 5.14 kcal/mol more stable than the pyrazole complex. In all, the selectivity and affinity of the oxazole tripods for the ammonium ions is thought to be a result of hydrogen bonding and the π -cation interaction (Figure VI.6). The three hydrogen bonds between the nitrogens of the oxazoles and the three hydrogens of the ammonium result in the selectivity for ammonium ions over potassium cations and π -cation interaction was calculated to add to the stability of the complex by ~ 16 kcal/mol.

The use of the oxazoline tripod as a receptor for alkylammonium ions was a natural extension and in the fall of 2000, the Kim group reported a series of oxazole tripods capable of binding *n*-BuNH₂, *s*-BuNH₂, *t*-BuNH₂ and PhCH₂NH₂.¹⁶ In most cases, high binding affinities ($\geq 10^5 \text{ M}^{-1}$) were observed. Interestingly, the authors found that several of the tripods showed

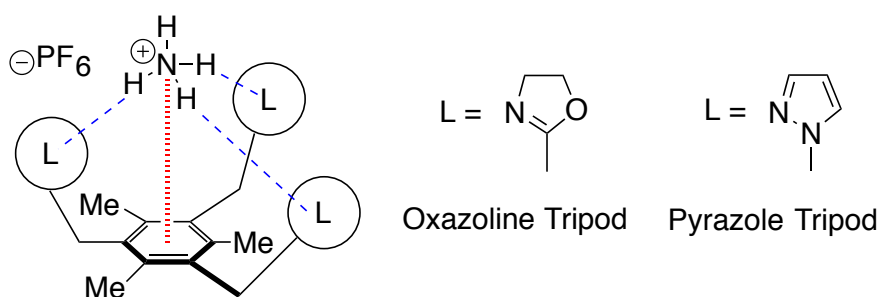
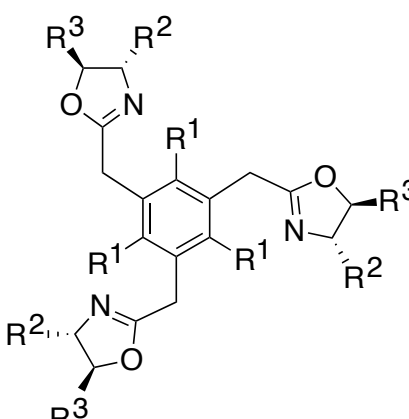


Figure VI.6: Binding interactions between ammonium and the tripods. The hydrogen bonds are shown in blue and the π -cation interaction in red.¹⁷

selective binding for *n*-BuNH₂ over *t*-BuNH₂ with the best of the tripods being 4000 times more selective for the linear *n*-butylammonium over the sterically demanding tert-butylammonium (Figure VI.7). The observed selectivity is due to the bulky phenyl rings of the oxazoline rings crowding the binding pocket for the ammonium cation and preventing binding of the larger tert-butylammonium salt. Enhancement of selectivity was also attributed to changing the benzene substituents from methyl groups to ethyl groups. The larger ethyl groups pre-organize the tripod by forcing the oxazoline units to the opposite face of the benzene thereby, the



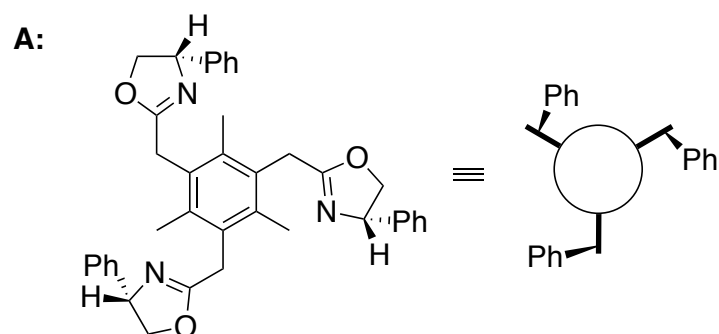
Entry	R ¹	R ²	R ³	Selectivity (<i>n</i> BuNH ₃ ⁺ / <i>t</i> BuNH ₃ ⁺)
1	Me	Ph	Ph	430
2	Et	Ph	H	2700
3	Et	Ph	Ph	4000

Figure VI.7: Oxazoline tripods for recognition of alkylammonium salts. The tripods shown exhibited selectivity towards *n*-butylammonium salt over the sterically demanding tert-butylammonium salt.¹⁶

binding pocket has formed prior to addition of the ammonium salt.

Finally, this selectivity with achiral butylammonium salts led the Kim group to hypothesize that the chiral tripod could be employed for selective recognition of chiral ammonium salts.^{18,19} The binding pocket of the tripod has inherent chirality from the chiral center or chiral centers of the oxazoline therefore, binding of a single enantiomer of the ammonium should be favored. Selective extraction of aromatic ammonium salts was achieved using a chiral oxazoline tripod bearing a phenyl ring (Figure VI.8 A). Figure VI.8 B shows the conformations of this tripod with the enantiomers of a chiral amine. Highlighted in blue is the key interaction leading to discrimination of the enantiomers of the amine. Binding of the (*R*) enantiomer of the amine is favored due to the favorable interaction of the oxazoline with small group as opposed to interaction with the large group which is observed with the (*S*) enantiomer. The authors do note that this system was not successful for chirality recognition with alkyl ammonium salts (alanine methyl ester, Figure VI.8 A). A pi-pi stacking interaction between the phenyl of the oxazoline and the aromatic portion of the ammonium salt is thought to increase stabilization of the complex with aromatic amines and enhance selectivity.

In recent years, a tripodal caged, oxazoline receptor was developed and showed enhancement of enantio-discrimination for alanine methyl ester. Also, the oxazoline tripod was used as fluorescence based sensor for chiral amines. Preferential binding for (*R*)-1-phenylethylamine over the (*S*) enantiomer was observed as indicated by greater enhancement of fluorescence intensity for the (*R*) enantiomer.



Ammonium Guest	Selectivity	Extraction (%)
	71(<i>R</i>):29(<i>S</i>)	82
	78(<i>S</i>):22(<i>R</i>)	60
	53(<i>S</i>):47(<i>R</i>)	41

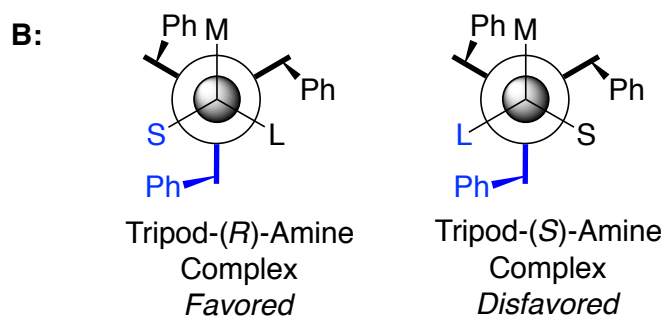


Figure VI.8: Enantioselective recognition of amines a tripodal host. **A:** Examples of selective binding with chiral amines. There is little selectivity with alanine methyl ester. **B:** Conformations of the diastereomeric tripod-amine complexes. (*R*) amine is favored due to the oxazoline-small group interaction in blue. Oxazoline-large group interactions makes binding of (*S*) amine unfavorable.¹⁸

VI.2: Design and Synthesis of a Tripodal Host for ECCD of Chiral Ammonium Ions

Based on the previous oxazoline tripod systems, it was hypothesized that an appropriate tripodal host molecule could be designed as a receptor and ECCD active host molecule for chiral ammonium salts. To maintain the high affinity for ammonium ions, the benzene floor would be retained to conserve the favorable π -cation interaction. Also, to retain the hydrogen bonding elements, the heterocyclic arms would also remain. However, rather than having a chiral receptor to resolve a racemic mixture of ammonium salts, a tripod for ECCD purposes would be achiral. Additionally, the heterocycle must be chromophoric for the tripod to have ECCD activity. Therefore, for the initial design, a benzoxazole was chosen as the heterocycle. Benzoxazole is achiral, the nitrogen atoms are hydrogen bond acceptors and the λ_{max} is 254 nm would render the complex chromophoric (see Figure VI.9 for the structure of the proposed tripodal host).

It is imperative to begin with an achiral host molecule for ECCD. The host should form an achiral binding pocket so that there is no inherent preference for binding either enantiomer of the ammonium. After complexation with a chiral ammonium salt, the point chirality of the ammonium will dictate the orientation of the oxazole arms of the tripod forcing the tripod to adopt either a clockwise (Λ complex) or counterclockwise helicity (Δ complex).²⁰ Therefore, there are two diastereomeric complexes possible for the ammonium-tripod complex. If an (*R*)-ammonium is complexed with the tripod, these diastereomers are the (*R*)- Λ complex and the (*R*)- Δ complex. The preferred complex and therefore, helicity of the tripod is that in which the steric interactions with the substituents at the chiral center are minimized.

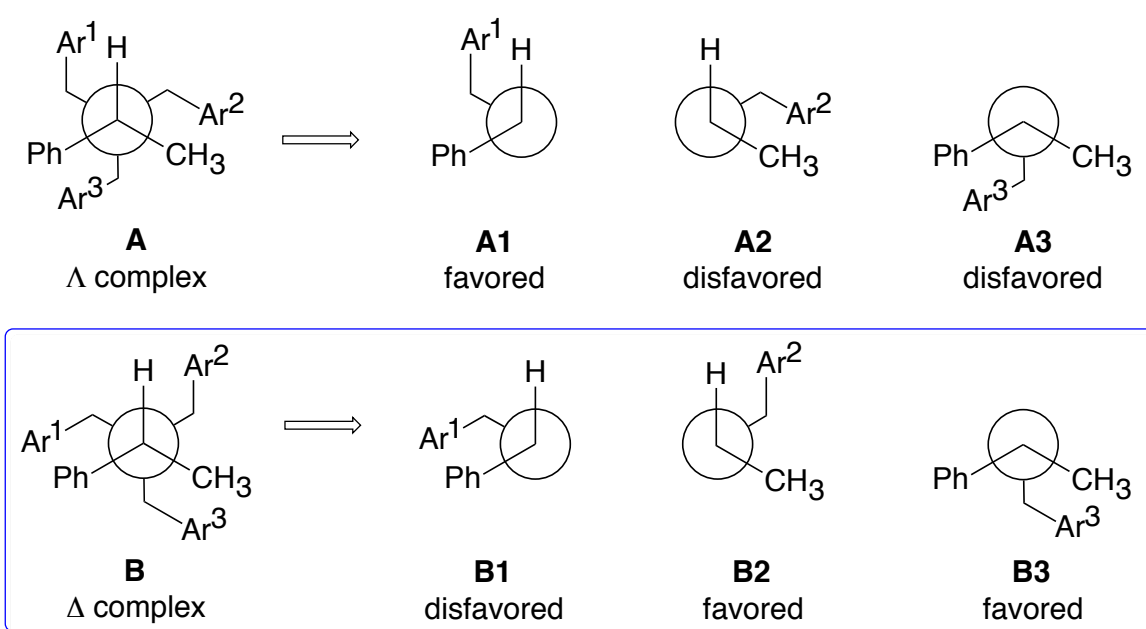
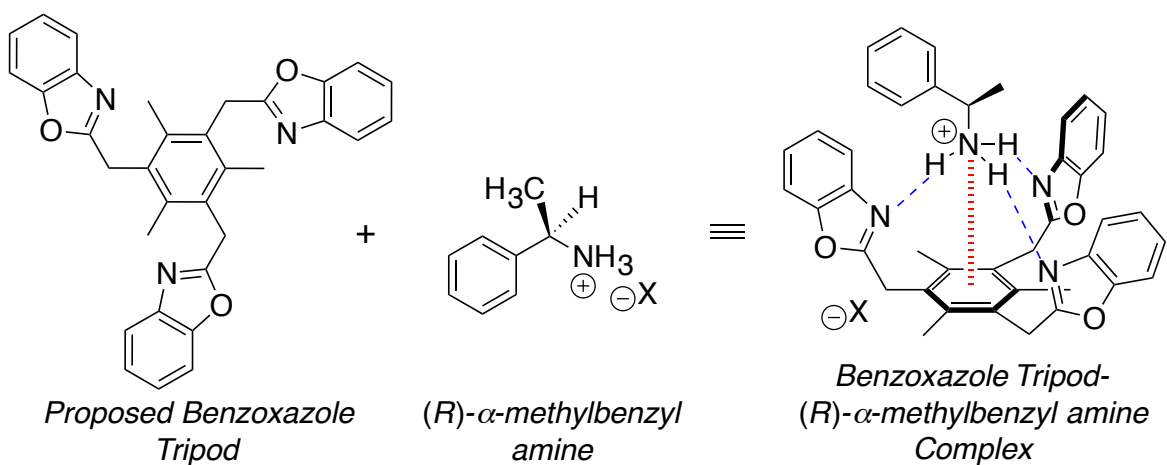


Figure VI.9: The proposed benzoxazole tripod for ECCD of ammonium salts. The complex with (R)- α -methylbenzylamine will have the π -cation interaction (red dashed line) and three hydrogen bonds (bold blue dashed lines) to stabilize the complex. **A** and **B** are the diastereomeric complexes of the tripod with (R)- α -methylbenzylamine. **A1-A3/B1-B3** consider the steric environment around each chromophore. For example, **A1** is favored due to the orientation of Ar¹ being toward the smaller H. Overall, **B** is the favored complex as this complex has fewer sterically disfavored interactions.²⁰

Figure VI.9 describes the two possible diastereomeric complexes of the achiral benzoxazole tripod with (*R*)- α -methylbenzylamine. To determine the favored diastereomer, the steric environment around each benzoxazole is considered as though the chromophores are independent system. For example, Figure VI.9.A1 determines if the steric environment about Ar¹ in the Λ complex is favorable. The large benzoxazole ring is oriented away from the bulky phenyl, towards the sterically smaller hydrogen therefore, this is favorable. However, A2 is disfavored because the benzoxazole is oriented away from the small hydrogen, toward the larger methyl. Overall, the Δ complex is favored with (*R*)- α -methylbenzylamine. This complex has more favorable steric interactions than the Λ complex with (*R*)- α -methylbenzylamine. For the enantiomer (*S*)- α -methylbenzylamine, the Λ complex would be favored. This means that the enantiomers of a single ammonium would induce the opposite helicity in the tripodal host. Furthermore, any ammonium having the same arrangement of small, medium and large groups as (*R*)- α -methylbenzylamine would be expected to favor the Δ complex. Thus, at least hypothetically, the tripod would be suitable host system for ECCD of ammonium salts.

Prediction of the sign of the ECCD signal for tripodal systems requires slightly different considerations than the porphyrin tweezer systems discussed in the previous chapters as there are now three chromophores that will interact to generate the signal. In 1970, Nakanishi and co-workers demonstrated that the configuration of cyclic triols could be determined from the ECCD of the corresponding tribenzoate.^{21,22} For the sugar tribenzoate, α -methyl-L-arabinopyranoside 2,3,4-tris(*p*-chlorobenzoate), a positive ECCD signal was observed (Figure VI. 10).²² To understand the positive sign, the chair form of the tribenzoate was considered. Then the expected sign for each pair of chromophores was determined. For all three pairs (2-3, 3-4,

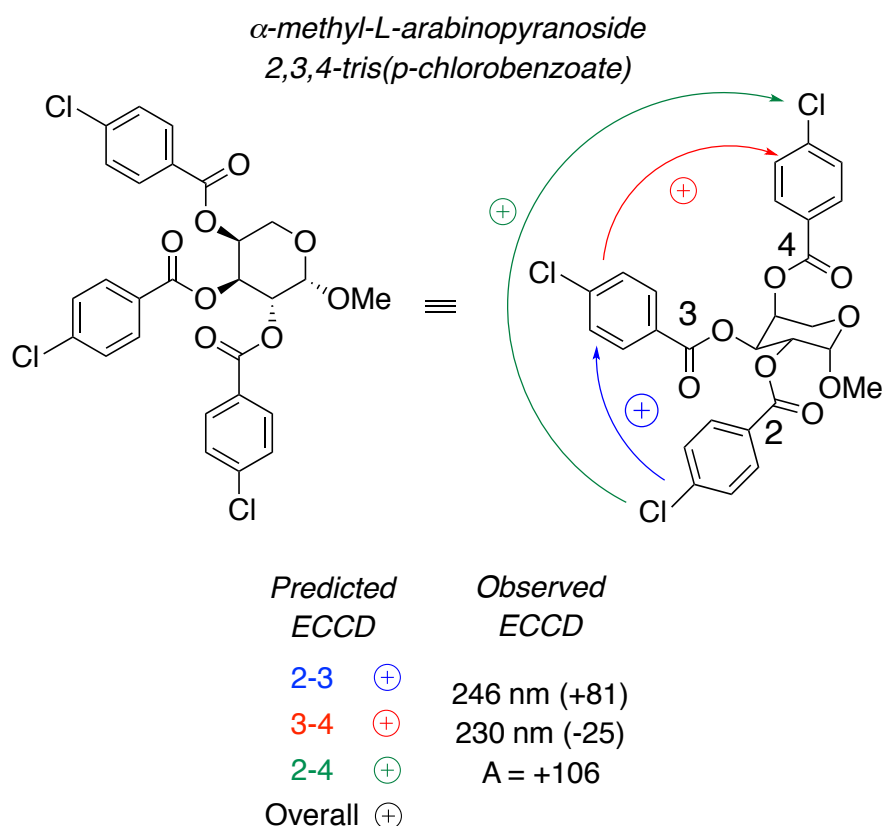


Figure VI.10: ECCD of a sugar tribenzoate. The overall ECCD signal is predicted by considering the ECCD signal of the three pairs of chromophores. Each pair is predicted to generate a positive ECCD therefore, the tribenzoate is expected to provide a positive ECCD.²²

2-4) a positive sign is expected as the benzoates are oriented in a clockwise fashion. With all three pairs expected to provide a positive signal, an overall positive sign for the tribenzoate was expected and observed. This pair-wise additivity of interacting chromophores was also used to successfully predict the expected ECCD signs for steroidal tribenzoates and sugar tetrabenzoates.

The pair-wise additivity rule would be applied to the tripod to predict the expected ECCD signal. When the tripod is in the Λ complex, the chromophores are oriented in a clockwise fashion. Clockwise helicity of two chromophores is expected to generate a positive

ECCD therefore, in the Λ complex there are three pairs of chromophores oriented in a clockwise fashion. All three pairs would provide a positive ECCD thus, the overall a positive ECCD would be expected. When the Δ complex is favored, all three chromophores are oriented in a counter-clockwise fashion. For each pair of interacting chromophores, a counter-clockwise helicity and negative sign are expected. A negative ECCD signal is predicted for the Δ complex.

The pair-wise additivity of chromophores can be applied to the proposed tripodal host to predict the sign of the ECCD signal based on the preferred helicity of the host-guest complex which can be correlated to the configuration of the bound amine (Figure VI.11). As discussed previously, the Δ complex is favored for (*R*)- α -methylbenzylamine. A negative ECCD couplet is predicted for the Δ complex therefore, it is expected that the ECCD observed for (*R*)- α -methylbenzylamine or any amine with the same configuration would be negative. The Λ complex and a positive ECCD signal would be expected for (*S*)- α -methylbenzylamine or any amine with the same configuration.

With a reasonable model for the tripod developed, synthesis of the 1,3,5-tris-(benzoxazolemethyl)-2,4,6-trimethylbenzene tripod was commenced. The synthesis of the tripod was designed such that the benzoxazole chromophores would be built through an acid catalyzed cyclization of *o*-aminophenol with 1,3,5-tris-(acetic acid)-2,4,6-trimethylbenzene in the final step and the trisacid would be synthesized from the commercially available mesitylene (Scheme VI.1 A).

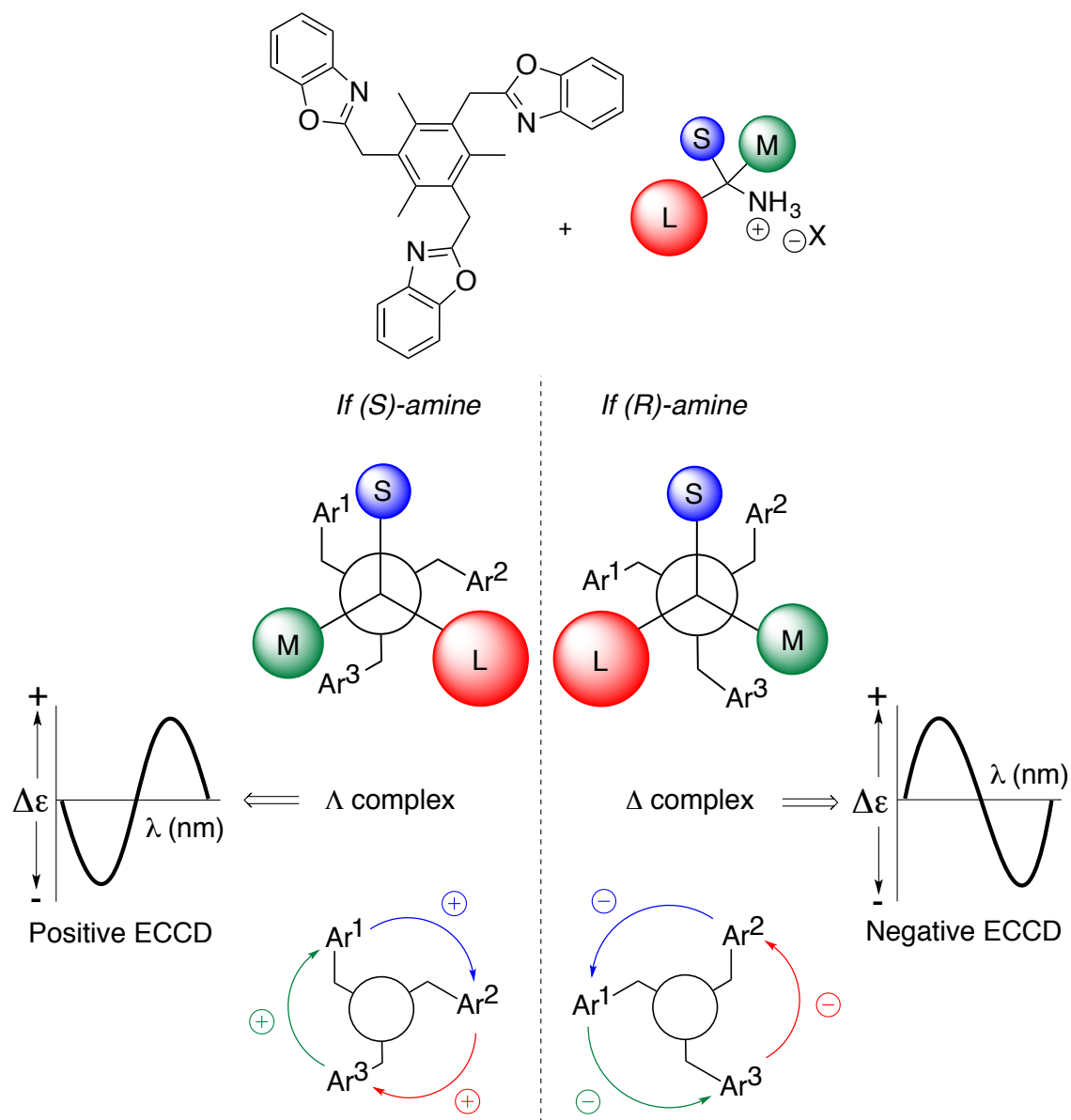
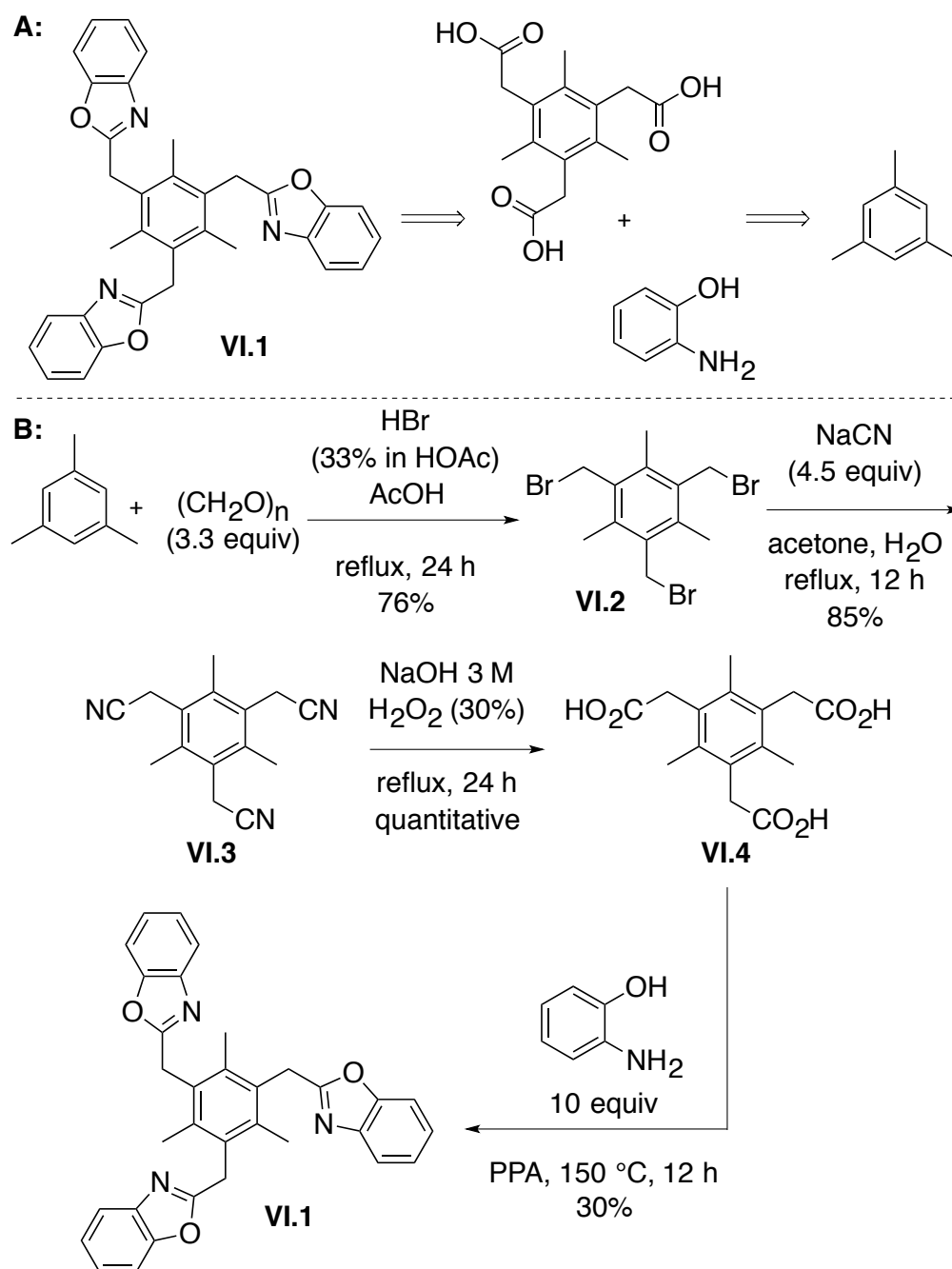


Figure VI.11: Proposed mnemonic for ECCD of chiral ammonium salts with the benzoxazole tripod. An (*S*) amine is expected to bind favorably with the tripod in the Λ complex. The Λ complex is expected to provide a positive ECCD curve based on pairwise additivity of chromophores. Therefore, an (*S*) amine is expected to generate a positive ECCD. The (*R*) amine is expected to give a negative ECCD.



Scheme VI.1: Synthesis of the benzoxazole tripod. **A:** Retrosynthesis from mesitylene.

B: Forward synthesis providing the tripod.

Synthesis of the tripod began with the installation of three bromomethylene units through Friedel-Crafts with paraformaldehyde in the presence of HBr (Scheme VI.1 B).²³ The

bromides were then replaced by cyano groups by substitution with NaCN.²⁴ Saponification of the cyano groups with NaOH and H₂O₂²⁵ provided the acid in 65% yield for the three steps. This synthesis of the trisacid has been scaled to 5 g without affecting the overall yield. With the acid in hand, the tripod was synthesized by a polyphosphoric acid (PPA) catalyzed cyclization with o-aminophenol.²⁶ This tripod was evaluated by UV spectroscopy (Figure VI.12) and found to have a $\lambda_{\text{max}} = 234 \text{ nm}$ with an $\epsilon \approx 60,000 \text{ L mol}^{-1} \text{ cm}^{-1}$ which matches well with the reported λ_{max} for benzoxazole (231 nm).²⁷ At high concentrations of tripod, charge transfer bands between 400 and 500 nm become intense.

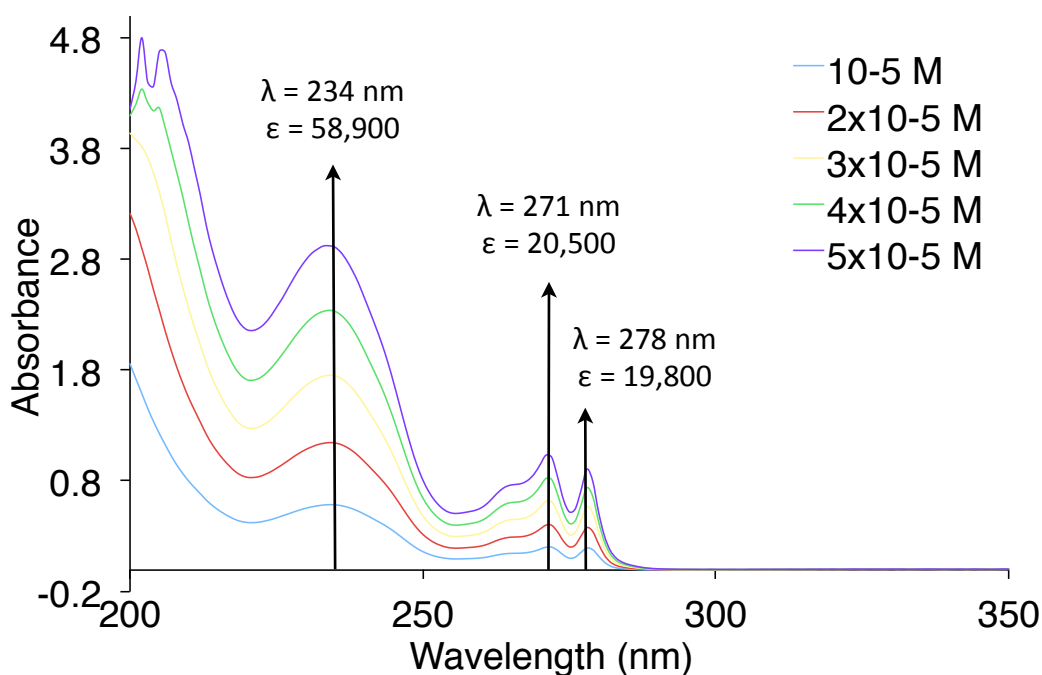


Figure VI.12: UV-vis spectrum of the benzoxazole tripod. Measurements taken in hexanes at room temperature.

VI.3: NMR Study of the Benoxazole Tripod with Chiral Amine Salts

Before attempting ECCD of an amine-tripod complex, the system was studied by NMR. If the complex formed, there should be chemical shift changes of the ammonium due to shielding or deshielding interactions with the aromatic benoxazole chromophores.

Initially, complexation with the hexafluorophosphate ammonium salt of α -methylbenzylamine was attempted following the extraction procedure established by Ahn and co-workers. First, the hydrochloric acid salt of the amine was generated by addition of hydrochloric acid to the amine in CH_2Cl_2 . The HCl salt was isolated by removal of CH_2Cl_2 . A 0.05 M solution of the amine salt with 1.2 equivalents of NaPF_6 was made in D_2O . NaPF_6 was used for anion exchange. The HCl salt of the amine is not chloroform soluble but hexafluorophosphate salts are typically soluble in organic solvents. By exchanging the anion, the salt should become soluble in chloroform. Next, 0.5 mL of the 0.05 M amine salt solution in D_2O was added to 0.5 mL of a 0.05 M solution of tripod in CDCl_3 . This was then centrifuged for an hour after which, the CDCl_3 was dried with a small amount of anhydrous Na_2SO_4 and the NMR was recorded. Unfortunately, after several attempts to follow this procedure with a variety of amines, the tripod/ammonium complex was observed only once by NMR. The complex observed was that for (*R*)- α -methylbenzylamine. Based on integrations this complex appeared to be 2:1 amine to tripod (Figure VI.13 B). Each of the amine signals shift upfield when in the complex.

With the limited success in forming the tripod-ammonium complex following the reported procedure, a new method of generating organic soluble ammonium salts was desired. Tetrafluoroborate salts of amines are also known to have high solubility in organic solvents and

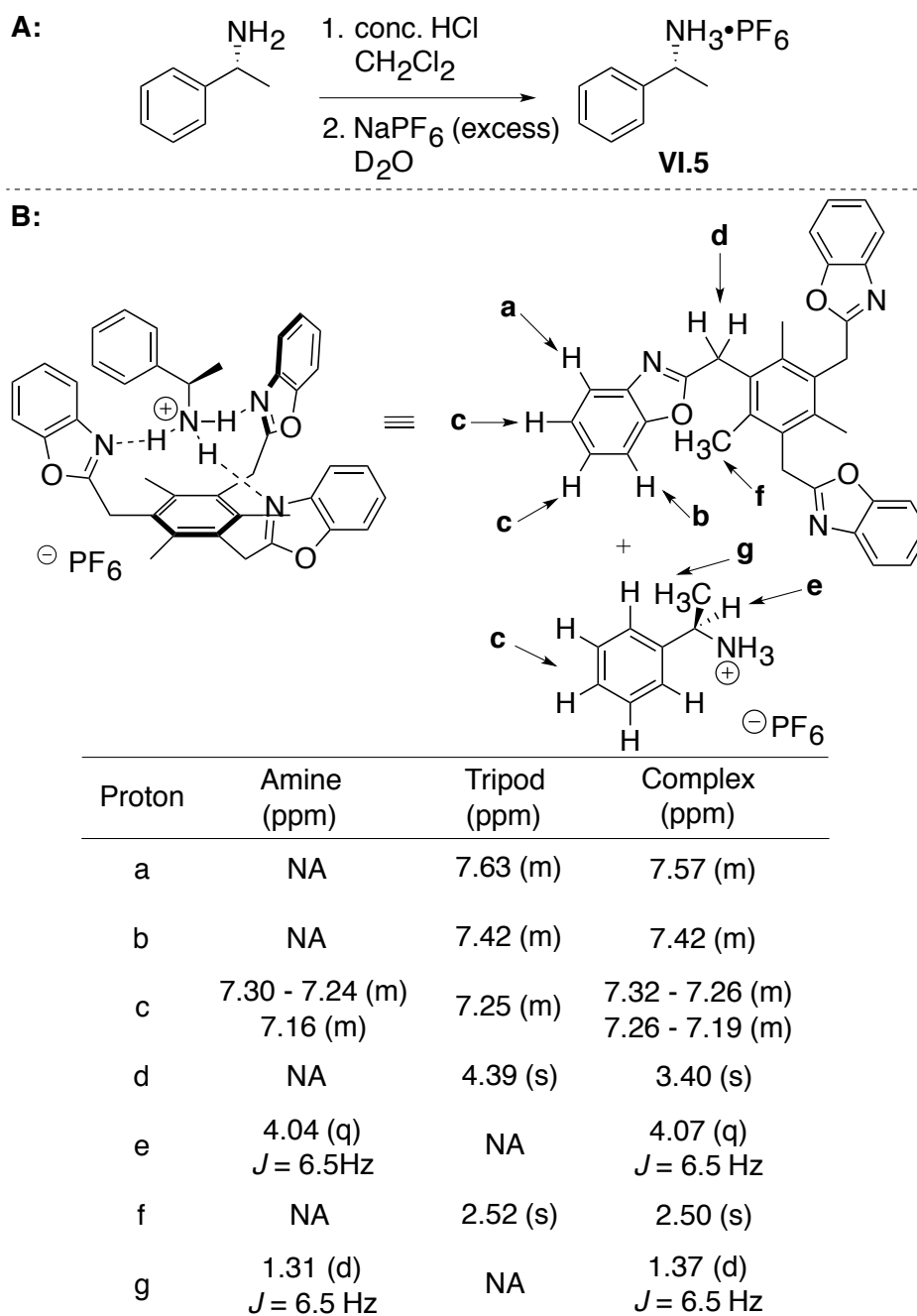


Figure VI.13: Complexation of (*R*)- α -methylbenzylammonium hexafluorophosphate with the benzoxazole tripod. **A:** Synthesis of the ammonium. **B:** Structure of the complex and NMR chemical shifts for the amine, tripod and complex in CDCl₃. All of the amine peaks shift upfield when in the complex. This is a 2:1 complex based on integration. NA = not applicable

can be easily accessed.²⁸ To the amine in methanol, tetrafluoroboric acid was added (Figure VI. 14 A). The ammonium was then extracted into CH₂Cl₂. With this procedure, the tetrafluoroborate salt of (*S*)-3-methyl-2-butamine was isolated then subjected to NMR study.

The NMR study was first conducted in CDCl₃. Upon addition of two equivalents of the amine to the tripod, there was no significant change in the chemical shifts of either the tripod or the ammonium. It was observed that the ammonium would begin to precipitate in CDCl₃. So, mixed solvent systems were evaluated to ensure solubility of the amine. Both CDCl₃/d⁶-acetone and CDCl₃/CD₃OD were chosen. Fortunately, in both solvent systems, evidence for complex formation was observed.

For CDCl₃/CD₃OD, when 1 equivalent of the amine was added, little change was observed for the amine protons (Figure VI.14 B). However, slight shifts of the tripod protons upfield was observed. With the addition of 2 equivalents of the amine, the tripod signals upfield shift by approximately 0.5 ppm, along with small upfield shifts for all the amine protons (~0.05 ppm). The upfield shift of the amine protons indicates that they are being shielded. This is expected as the amine is situated in the shielding cone of the benzene floor and possibly the shielding cone of the benzoxazole.

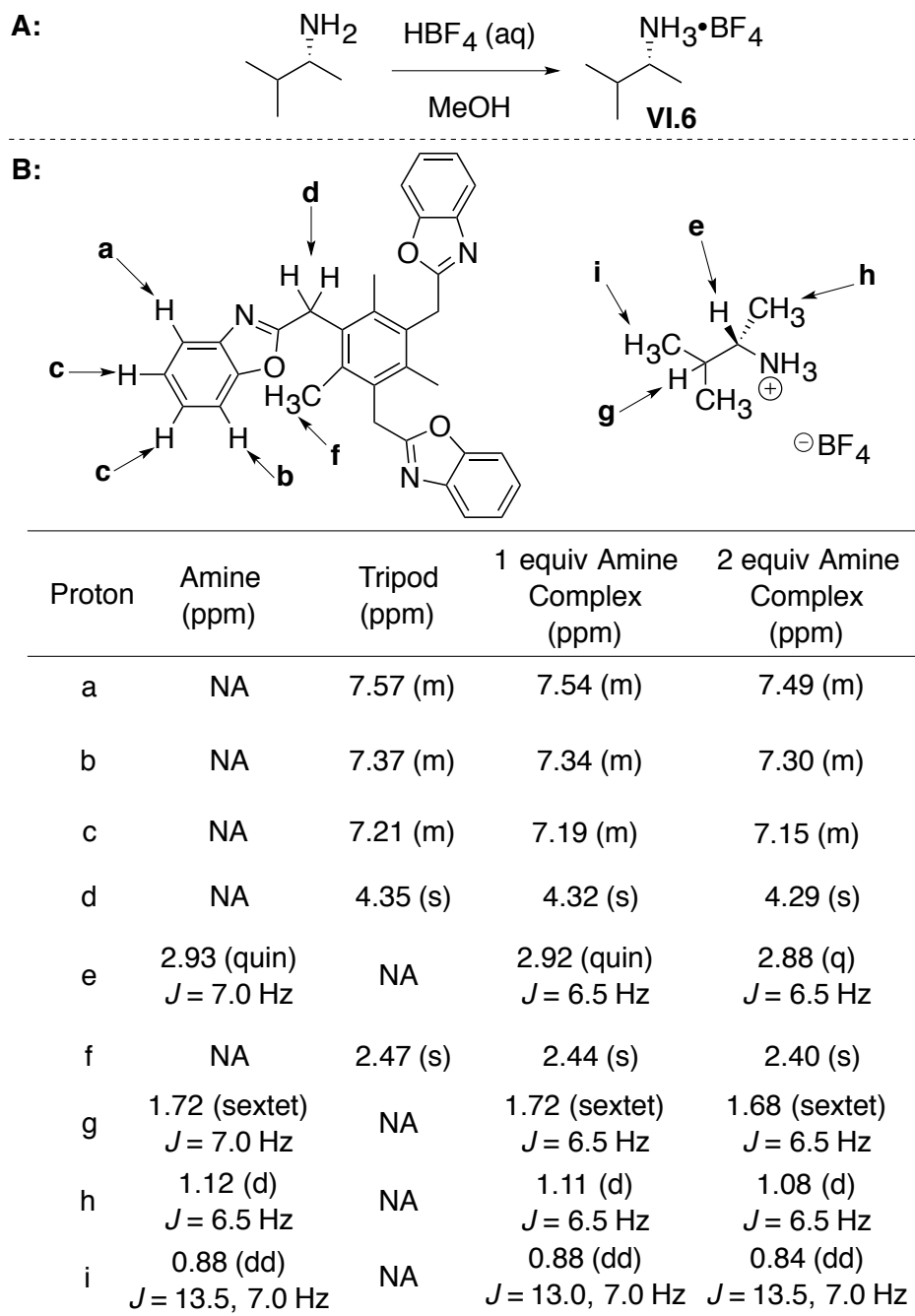
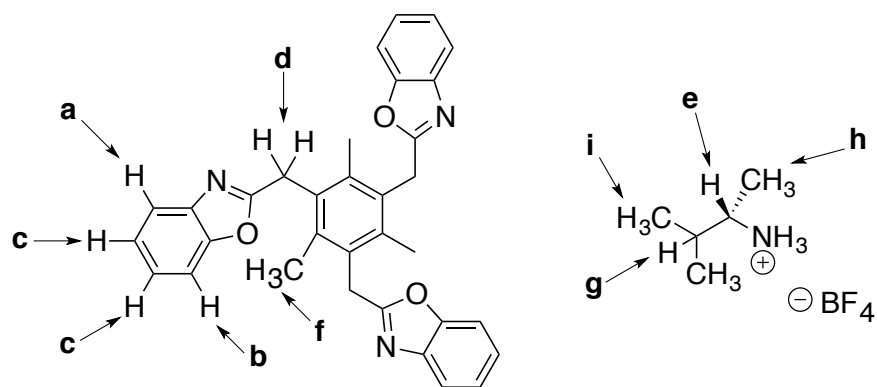


Figure VI.14: NMR study of the benzoxazole tripod with (*S*)-3-methyl-2-butamine tetrafluoroborate in CDCl₃/CD₃OD. **A:** Synthesis of the ammonium salt. **B:** Table of NMR data. 1 equivalent showed little change however, with 2 equivalents all of the tripod and amine signals shift upfield indicating possible complex formation. NA = not applicable

In $\text{CDCl}_3/\text{d}^6\text{-acetone}$, at 1 and 3 equivalents of amine in a solution of the tripod, there were two sets of peaks corresponding to the amine (Figure VI.15). One set correlated well with the signals for the ammonium salt. The second set of peaks were shifted relative to the ammonium. The amine methine proton showed the largest change being downfield shifted by 0.4 ppm. The methyl doublet was also downfield shifted but to a lesser extent. The isopropyl methine and methyl protons showed a slight upfield shift. At four equivalents of amine, the amine chemical shifts match the chemical shifts of the ammonium which would indicate that the complex has disintegrated. With one equivalent of the ammonium, the integrations of the amine methine peaks shows that half of the ammonium is interacting with the tripod and half is not. The same is observed with 3 equivalents of the ammonium. This is interesting as again it could suggest that although the amine interacts with the tripod it is not in the 1:1 complex that is desired. Also, a downfield shift of the ammonium methine is concerning. It is predicted that in a 1:1 complex, this methine should be situated in the shielding cone of the benzene core. Therefore, there is evidence of interaction with the tripod however, likely not in a 1:1 complex.

Encouraged that there was some type of complex formation between the benzoxazole tripod and the ammonium salt, a search to find the optimal conditions for ECCD analysis of the complex was undertaken. Unfortunately, after changing of solvent (CHCl_3 , CH_3OH , hexanes), concentration (10^{-5} M to 10^{-4} M) and temperature (-10°C , 0°C , rt), ECCD was not observed with this system. However, with NMR evidence suggesting complex formation, optimization of the tripod should be undertaken in the future.



Proton	Amine (ppm)	Tripod (ppm)	1 equiv Amine Complex (ppm)	3 equiv Amine Complex (ppm)	4 equiv Amine Complex (ppm)
a	NA	7.54 (m)	7.50 (m)	7.38 (m)	7.41 (m)
b	NA	7.33 (m)	7.30 (m)	7.20 (m)	7.22 (m)
c	NA	7.16 (m)	7.17 (m)	7.02 (m)	7.05 (m)
d	NA	4.31 (s)	4.27 (s)	4.18 (s)	4.20 (s)
e	3.19 (quin) $J = 6.5\text{ Hz}$	NA	3.66 (quin) $J = 6.5\text{ Hz}$ 3.17 (quin) $J = 6.5\text{ Hz}$	3.48 (quin) $J = 6.5\text{ Hz}$ 3.04 (quin) $J = 6.0\text{ Hz}$	3.12 (quin) $J = 6.0\text{ Hz}$
f	NA	2.44 (s)	2.40 (s)	2.30 (s)	2.32 (s)
g	1.88 (sextet) $J = 6.5\text{ Hz}$	NA	1.89 (m)	1.77 (sextet) $J = 7.0\text{ Hz}$ 1.72 (sextet) $J = 6.5\text{ Hz}$	1.80 (sextet) $J = 6.5\text{ Hz}$
h	1.22 (d) $J = 6.5\text{ Hz}$	NA	1.26 (d) $J = 7.0\text{ Hz}$ 1.22 (d) $J = 7.0\text{ Hz}$	1.10 (d) $J = 6.5\text{ Hz}$ 1.08 (d) $J = 6.5\text{ Hz}$	1.15 (d) $J = 6.5\text{ Hz}$
i	0.91 (dd) $J = 16.0, 7.0\text{ Hz}$	NA	0.90 (dd) $J = 14.0, 7.0\text{ Hz}$ 0.86 (dd) $J = 17.0, 7.0\text{ Hz}$	0.79 (dd) $J = 10.0, 7.0\text{ Hz}$ 0.73 (dd) $J = 21.0, 6.5\text{ Hz}$	0.82 (dd) $J = 15.5, 7.0\text{ Hz}$

Figure VI.15: NMR study of the benzoxazole tripod with (S)-3-methyl-2-butamine tetrafluoroborate in $\text{CDCl}_3/\text{d}^6\text{-acetone}$. NA = not applicable

VI.4: Conclusions and Suggestions for Future Studies

There are several ways in which the tripod could be further optimized to an ECCD active host molecule. One major limitation of the benzoxazole tripod is the λ_{max} of the chromophore. The absorbance of benzoxazole is close to the absorbance of chromophores commonly encountered in organic compounds. The expected ECCD for benzylamine with the benzoxazole tripod would be complicated by coupling of the benzoxazole chromophores with the benzene of the amine. A tripod with a red shifted chromophore would prevent coupling with the guest substrate. To this end, extending the conjugation of the chromophore would red shift the absorbance. Naphthoxazoles ($\lambda_{\text{max}} \approx 300 \text{ nm}$),²⁹ anthroxazole, phenanthroxazole ($\lambda_{\text{max}} \approx 330 \text{ nm}$)³⁰ should be considered.

Modification of the heterocyclic portion of the chromophore could be another route of optimization. As shown, imidazole based chromophores should form stronger hydrogen bonds with the ammonium than oxazole due to the increased basicity of the heterocycle.¹⁷ Additionally, thioxazole containing chromophores could also be considered as the basicity of thioxazole (2.5) lies between that of the oxazole (0.8, least basic) and imidazole (4.9, most basic).

Finally, as discussed above, Ahn and co-workers observed enhanced binding affinities for alkylammoniums when triethylbenzene was used for the floor of the tripod.¹⁶ They hypothesized that the tighter binding was due to pre-organization of the binding pocket. Therefore, tripods with the triethylbenzene core should be considered. If pre-organization of the pocket has been shown to enhance binding affinities, then it may also promote formation

of the 1:1 tripod-ammonium complex. Mr. Jun Zhang has already begun work on tripods with triethylbenzene floor.

VI.5: Experimental Procedures

VI.5.1: General Procedures

Where it is stated that dry CH_2Cl_2 or dry toluene was used, the solvent was distilled over CaH_2 . Dry THF and diethyl ether were obtained by distillation from sodium benzophenone ketyl. All other reagents, unless indicated otherwise, were purchased from commercial sources.

Thin layer chromatography was performed on Merck aluminum sheets coated with silica gel (0.2mm thickness). Potassium permanganate, anisaldehyde, polymolybdic acid and UV were used for visualization. Silica chromatography was performed using Dynamic Adsorbents Inc Flash Silica Gel 32-634.

^1H NMR was recorded with Varian Inova 300 or 500 MHz instruments in CDCl_3 . The reported ^1H NMR chemical shifts are relative to the CDCl_3 line (7.24 ppm) and the ^{13}C NMR chemical shifts are relative to the central CDCl_3 line (77.0 ppm). ^{19}F NMR was recorded on the 300 MHz instrument. Mass spectra were recorded using Mass Spectrometry Laboratory using micromass VG-70 mass spectrometer. UV/Vis spectra were recorded on a Perkin-Elmer Lambda 40 spectrophotometer. The CD spectra were recorded on a Jasco J-810 spectropolarimeter equipped with a Neslab 111 temperature controller.

VI.5.2: Synthesis and Characterization Data for Substrates

1,3,5-tris-(benzoxazolemethyl)-2,4,6-trimethylbenzene (**VI.1**): A 50 mL round bottom flask was equipped with a stir bar and reflux condenser. To the flask, PPA (25 mL), *o*-aminophenol (1.855 g, 16.98 mmol, 10 equiv) and **VI.4** (500 mg, 1.698 mmol, 1 equiv) were added. The mixture was

heated to 150 °C, while stirring under N₂ for 24 hours. The black mixture was cooled to room temperature then poured of 250 mL of ice water while stirring. The resulting mixture was neutralized with sodium bicarbonate then the crude product was collected by vacuum filtration. The black tar collected was dissolved in hot ethanol and the insoluble solids were removed by vacuum filtration. The filtrate was concentrated under reduced pressure and this crude mixture was purified via column chromatography (100% EtOAc). The product was isolated as an off-white solid (173 mg, 20%).

(**VI.1**): ¹H NMR (CDCl₃, 500 MHz): δ 7.63 (3H, m), 7.42 (3H, m), 7.25 (6H, m), 4.39 (6H, s), 2.52 (9H, s).

¹H NMR (CDCl₃/CD₃OD, 500 MHz): δ 7.57 (3H, m), 7.37 (3H, m), 7.21 (6H, m), 4.35 (6H, s), 2.47 (9H, s).

¹H NMR (CDCl₃/d⁶-acetone, 500 MHz): δ 7.54 (3H, m), 7.33 (3H, m), 7.25 (6H, m), 4.31 (6H, s), 2.44 (9H, s).

¹³C NMR (CDCl₃, 125 MHz): δ 164.9, 150.9, 141.4, 136.4, 130.9, 124.5, 124.1, 119.8, 110.5, 30.6, 17.4.

Melting Point: 215-217 °C

1,3,5-tris-(bromomethyl)-2,4,6-trimethylbenzene (**VI.2**):²³ Mesitylene (5.787 mL, 5 g, 0.04 mol, 1 eq) and paraformaldehyde (3.96 g, 0.132 mol, 3.3 equiv) were added to a 100 mL round bottom flask equipped with a stir bar and reflux condenser. To this, glacial acetic acid (20 mL) and hydrobromic acid (33% in acetic acid, 29 mL) were added and the mixture was heated to 95 °C under N₂ while stirring. Heating continued for 24 hours. The solution was allowed to cool to

room temperature and then was poured into water (20 mL) while stirring vigorously. The precipitate was filtered to give the product **VI.2** as a white solid in 76% yield (12.1 g).

(**VI.2**): ^1H NMR (CDCl_3 , 300 MHz): δ 4.55 (6H, s), 2.44 (9H, s).

^{13}C NMR (CDCl_3 , 75 MHz): δ 137.9, 133.2, 29.9, 15.4.

Melting Point: 180-181 °C

1,3,5-tris-(cyanomethyl)-2,4,6-trimethylbenzene (**VI.3**): In a 500 mL round bottom flask with stir bar and reflux condenser, **VI.2** (5 g, 12.5 mmol, 1 eq) and sodium cyanide (2.75 g, 56.25 mmol, 4.5 equiv) were added to acetone (125 mL, 0.1 M solution of **VI.2**). To this mixture, water (60 mL) was added to cause the solution to become turbid. Following, another 3 mL of acetone was added and the mixture was heated to reflux under N_2 , while stirring for 12 hours. The resulting solution was cooled to room temperature and poured over ice water (200 mL). The precipitate was filtered to yield the product **VI.3** as a white solid in 85% yield (2.5 g).

(**VI.3**): ^1H NMR (CDCl_3 , 300 MHz): δ 3.71 (6H, s), 2.44 (9H, s).

^{13}C NMR (CDCl_3 , 75 MHz): δ 135.9, 127.6, 116.7, 19.1, 17.1.

Melting Point: 249-252 °C

1,3,5-tris-(ethanoic acid)-2,4,6-trimethylbenzene (**VI.4**):

In a 500 mL round bottom flask **VI.3** (2 g, 8.4 mmol, 1 equiv) was dissolved in sodium hydroxide (3 M, 225 mL) and hydrogen peroxide (90 mL) while stirring. The solution was heated to reflux under N_2 while stirring for 24 hours. The solution was cooled to room

temperature and then acidified (pink to blue litmus) with hydrochloric acid (3 M). Water was added to dissolve any precipitate that had formed. The resulting solution was extracted with ethyl acetate (350 mL, 3 xs). The organic layers were then combined and the solvent was removed under reduced pressure to yield the desired product **VI.4** as a yellow solid in 66% yield (1.63g).

(VI.4): ^1H NMR (CDCl_3 , 300 MHz): δ 11.58 (3H, br s), 3.54 (6H, s), 2.13 (9H, s).

^{13}C NMR (CDCl_3 , 75 MHz): δ 173.3, 134.8, 129.9, 36.1, 16.7.

Melting Point: 262-265 $^{\circ}\text{C}$

(R)- α -methylbenzylammonium hexafluorophosphate (VI.5): To a solution of *(R)*- α -methylbenzylamine (15.9 μL , 15.2 mg, 0.125 mmol, 1 equiv) in CH_2Cl_2 in a 20 mL vial, 0.05 mL of concentrated hydrochloric acid was added then the solution was stirred for an hour. The solvent was removed under reduced pressure and the salt was dissolved in H_2O and sodium hexafluorophosphate (25.2 mg, 0.15 mmol, 1.2 equiv) was added and stirred for 1 hour. The water was extracted with CH_2Cl_2 (10 mL, 3 xs) and then the organics were dried with Na_2SO_4 followed by removal of the solvent under reduced pressure to give the salt as a colorless oil.

(VI.5): ^1H NMR (CDCl_3 , 500 MHz): δ 7.30 - 7.24 (4H, m), 7.16 (1H, m), 4.04 (1H, quartet, $J = 6.5$ Hz), 1.31 (3H, d, $J = 6.5$ Hz).

(S)-3-methyl-2-butammonium tetrafluoroborate (**VI.6**):

In a 20 mL vial, (S)-3-methyl-2-butamine (5 mg, 0.06 mmol, 1 equiv) was dissolved in methanol (3 mL) then tetrafluoroboric acid (48% aq, 3 mL) was added. The solution was stirred for 30 minutes then was extracted with CH₂Cl₂ (10 mL, 3 xs). The CH₂Cl₂ was combined and dried with Na₂SO₄ then the solvent was removed under reduced pressure to provide the desired product as a colorless oil.

(**VI.6**): ¹H NMR (CDCl₃/d⁶-acetone, 500 MHz): δ 3.19 (3H, quintet, *J* = 6.5 Hz), 1.88 (1H, sextet, *J* = 6.5 Hz), 1.22 (3H, d, *J* = 6.5 Hz), 0.91 (6H, dd, *J* = 16.0, 7.0 Hz).

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